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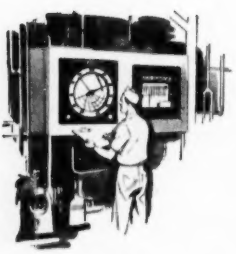

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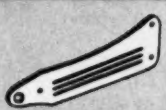

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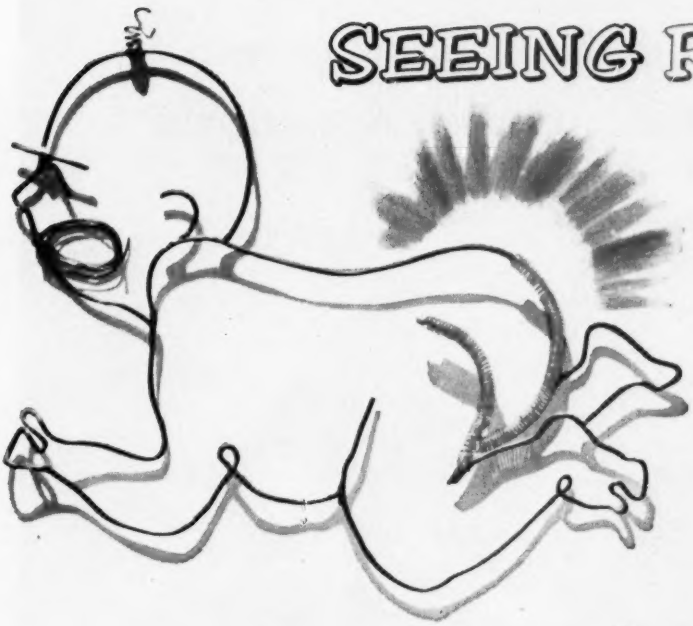

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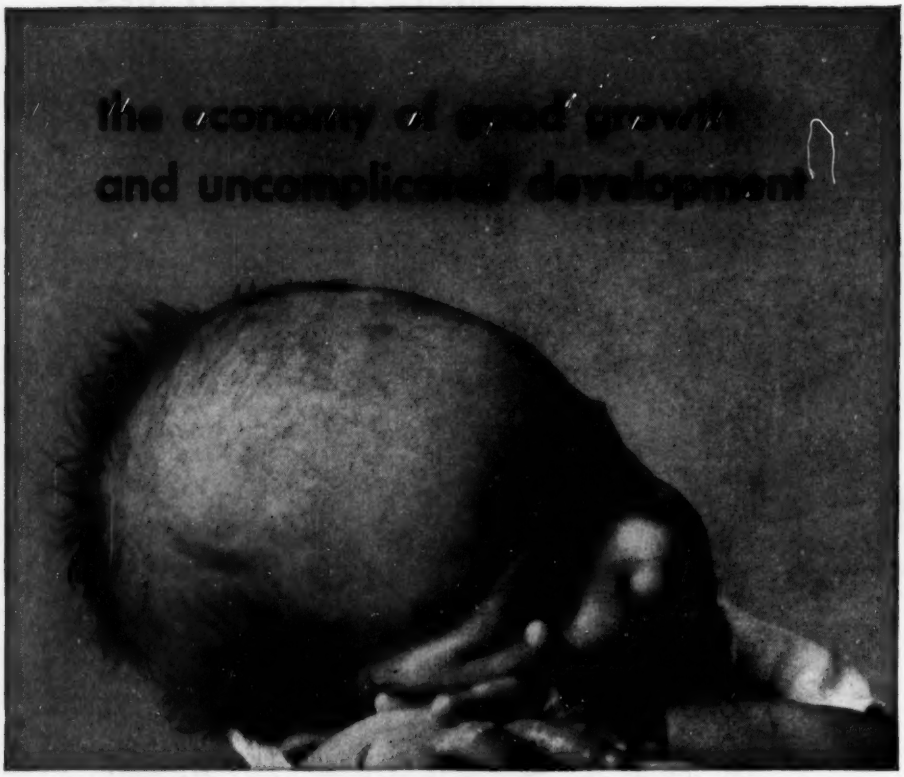

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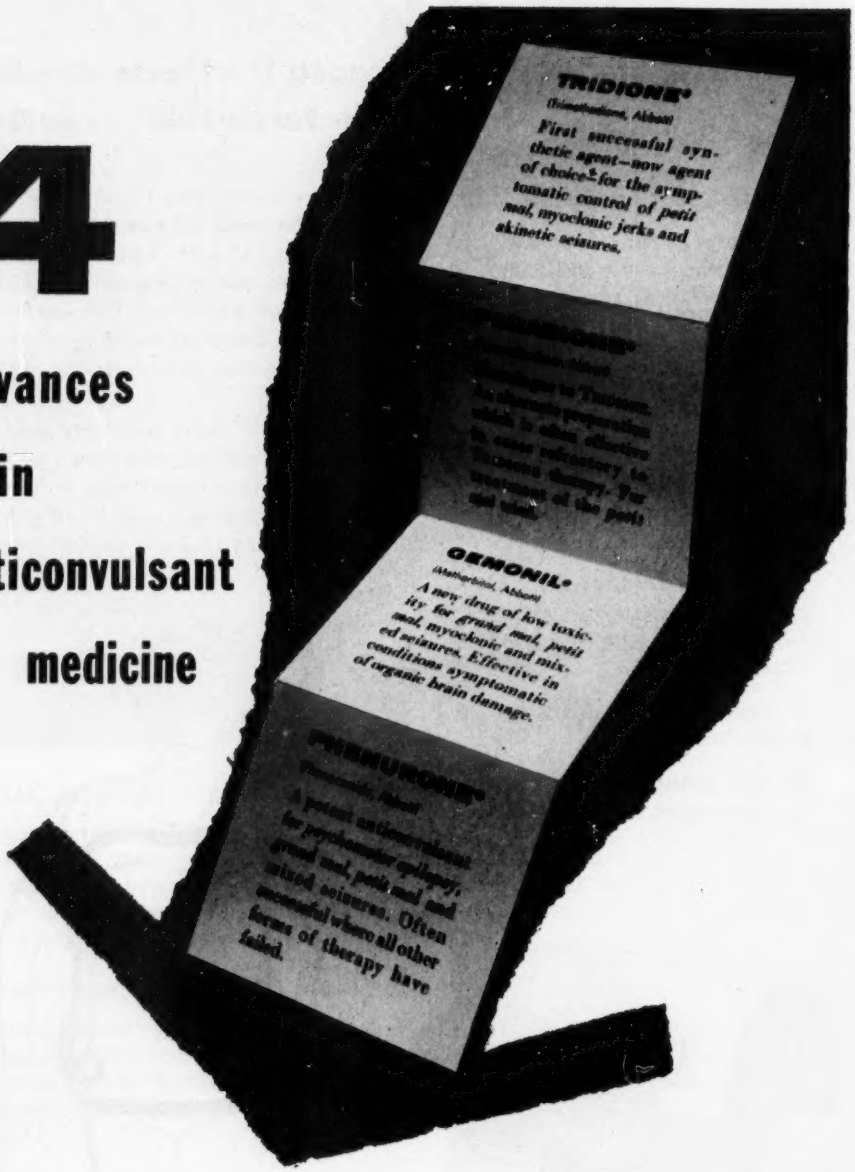
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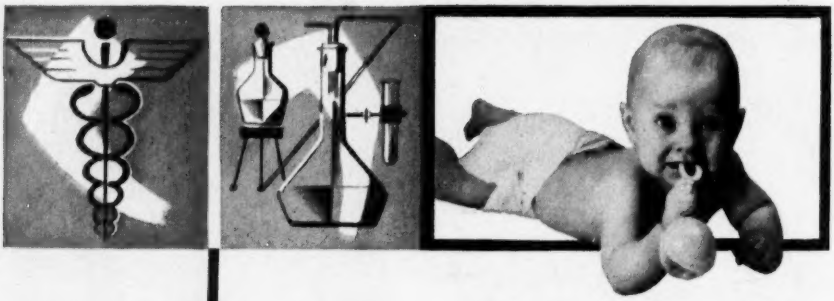

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A. M. A.
American Journal of Diseases of Children

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WEIGHT OF EVIDENCE

RUSTIN McINTOSH, M.D.
NEW YORK

PART OF the clinician's job is to gather evidence; another part is to interpret it. Practically all of us are teachers of pediatrics, at least in the bonds of the Hippocratic oath if not actually on a university payroll. As such we have the dual responsibility of evaluating clinical evidence in the course of our own work with patients and of teaching the process of evaluation to the degree that we consciously strive to perfect it. In current practices of clinical teaching, the indoctrination of students into the various modalities of gathering evidence is clearly planned and well executed. In history taking, in physical examination, and in the application of laboratory diagnostic aids to the problem in hand, the student can to a very large extent substitute method and conscientious application of a design of inquiry for actual experience in dealing with sick people. That is to say, he can effect this substitution so far as the collection of evidence is concerned. How well does he fare in interpretation? Or, to put the same question from another point of view, how successful is clinical instruction, either at the undergraduate student level or even with interns and residents, in guiding the student to a judicious weighing of the evidence he has assembled and in sorting the gold from the dross?

The question implies a suspicion that things can well be improved. As a first step it may be appropriate to make a rough dissection of the mental process of interpretation, of the evaluation of an item of evidence related to a clinical problem. In general terms, any such piece of evidence has to be put through comparable processes in the mental mill, whether it is an aspect of the history, a physical finding, images on a sensitized film, or a measurement made in a laboratory. Half a dozen such separate processes can be listed immediately, each of which comes into play in the sizing up of evidence.

First, there is a qualitative aspect. Of the various sounds one may hear in listening over the precordium, a pericardial friction rub sets itself apart from all other sounds referable to the heart itself, to respiration, or to artifacts produced by movement of the stethoscope bell on the skin. Rales of certain types carry definite implications.

Second, each sign has a quantitative aspect, and we recognize that, on the whole, measurements which we can make in a laboratory lend themselves to progressive refinement, while those which are bound to the bedside have fairly fixed limits of

From the Babies Hospital and Department of Pediatrics, Columbia University College of Physicians and Surgeons.

Presidential address delivered at the 64th Annual Meeting of the American Pediatric Society, Buck Hill Falls, Pa., May 3, 1954.

accuracy. By and large, laboratory measurements have a way of being more readily compared with one another and with normal standards of reference. Comparison of most clinical signs suffers by remaining a highly personal experience on the part of the examiner. I for one derive little ideographic satisfaction from trying to describe the force of a cardiac murmur as Grade 1, 2, 3, or 4, or from expressing clubbing of the fingers in terms of + or ++++. It is correspondingly difficult in clinical teaching to find words which will clarify to the student normal bowel sounds, as heard through the abdominal wall, against which he can compare exaggerated or depressed peristaltic activity. However, even granting the difficulty of weighing physical signs in objective terms, one cannot safely imply that all laboratory measurements are of superior validity, and enough must be learned of the technical procedures involved to appreciate sources of error and the magnitude of potential deception—all of which must be encompassed in quantitative evaluation.

Third, with every bit of evidence, the biological background must be taken into consideration—the setting, the host, particularly the age of the host, the chronological frame of reference in which the pediatrician must be thoroughly at home if he is to be effective. For illustration, a Babinski sign is a normal phenomenon at certain ages, neurologically significant at others.

Fourth, the significance of a sign is measured to some extent by the associated signs or symptoms. A blowing systolic murmur taken by itself is too common a phenomenon in childhood to carry much weight, and, similarly, an elevated sedimentation rate has many possible causes, but a systolic murmur associated with a conspicuously elevated sedimentation rate means, for practical purposes, rheumatic fever until proved otherwise.

Fifth, it is part of the clinician's stock in trade to be familiar with the probabilities that a given sign or symptom or laboratory finding is associated with a specific disease or syndrome. Unfortunately for the student of medicine, only a few items prove to be pathognomonic, like the finding of malaria parasites in red cells, or the cultivation of pathogenic bacteria in blood culture. Even so specific a diagnostic aid as the intracutaneous tuberculin test has its sources of error and, even when positive, tells nothing about location or state of activity of the disease process. Nowadays false-positive serologic tests for syphilis probably outnumber true positives in ordinary hospital experience.

The medical student in his rather pathetic quest for pathognomonic signs and tests is virtually doomed to frustration; but so long as the search is on, he is apt to find himself quite impatient with discussion of probabilities. In what diseases or in what circumstances, for example, are the epitrochlear lymph nodes palpable, and what are the relative frequencies of this association? A few highly successful teachers deliberately equip themselves for teaching clinical probabilities in actual percentages, after the manner of Richard Cabot; actually, however, most practitioners who are called on to teach are discouraged from attempting these quantitative refinements, partly because they imply a degree of accuracy not inherent in the data, partly because of the rapid changes which take place in morbidity experience.

We all recognize the fluctuations in the picture of pneumonia to which we have had to adjust our thinking in the past 15 years—fluctuations in pathogenesis, symptomatology, course, and prognosis, not to mention treatment, which is another sub-

ject in itself. These are changes to which clinicians everywhere have had to adapt their outlook in dealing with patients of all ages. On the whole, the degree of change in community morbidity over the years has probably been more violent, more far-reaching and more subversive in the age range of pediatric practice than in internal medicine. One cannot avoid the necessity of cultivating an active interest in clinical probabilities in pediatrics, even though it is in some degree futile to attempt to keep one's calculated percentages constantly up to date. The need for such general concepts keeps cropping up.

Finally, the evaluation of clinical evidence comes to the hypothetical synthesis of fragments into an integrated whole, the piecing together of blocks to form the outline of a familiar disease picture or syndrome. Individual items, one by one, and then group by group, are tested for fit against a background framework of first one clinical entity then another in a search for conformity without distortion. If conformity with a known picture is not attainable, we look for gaps to be filled, for additional evidence to be sought in a planned diagnostic and therapeutic attack. One of three results ensues: (1) the chain of evidence proves convincing—a specific diagnosis is apparent; (2) the field of possible choices becomes narrowed to manageable dimensions and additional diagnostic and prognostic tests can be applied aptly rather than haphazardly; (3) a most rare goal but one always attainable with the application of newly available resources guided by an open mind, the delineation of an undescribed clinical phenomenon, a new syndrome.

Here, then, in summary are six separate balances in which each fragment of evidence gathered during the study of a clinical problem is to be weighed, often simultaneously and even as one goes along on a busy round, sifting and sorting as the history emerges and as physical signs are sought. The fact that the clinician in practice appears to act instinctively in reaching a judgment serves only as a deceit, making the process appear simpler than it is or can possibly be. From reflection on what is involved in the evaluation of clinical evidence and from these several dissections, there emerge no obvious conclusions as to how best to proceed in our efforts to advance the art of interpretation and to transmit to others the knowledge gained.

It seems clear that the scope of the clinical lecture is limited, that case work and more case work must be the foundation of clinical teaching. On this one can then build with textbook study, assigned reading in pertinent periodical literature, and discussions between student and instructor, with the individual patient kept constantly in mind as the reference point. The student must be helped to experience with his own senses the validity of clinical evidence and in doing so to learn what weight to give it. A mass described is never the same vivid experience as is a bulging outline seen, a contour and a consistency felt, a mobility tested, with all that this may mean to the proprioceptive end-organs.

To me it appears a disservice to students if we encourage them in their search for pathognomonic signs, rather than have them view all aspects of a patient's problem as an entity; and it is particularly deplorable if through misplaced focus of attention we let them infer that a clinical problem can be appropriately described in a series of laboratory reports. To some students fresh from their courses in the medical sciences and fired with zeal to put clinical pediatrics on an accurate quantitative

basis, the identification of Mongolian idiocy represents the paradigm of frustration—a situation in which no one sign is diagnostic and in which all the accessory aids one can bring to bear, including x-ray, carry less weight than does the impression gained on simple inspection. Here is the problem of the weight of evidence in a nutshell. If, then, students are to be coaxed to accord more judicious consideration to information which they may glean from history and from physical examination, we owe them guidance in those elusive areas of clinical probabilities and the influence of age on normal behavior and on behavior during illness, the pediatrician's special preserve.

Effective judgment in clinical evaluations being virtually the last goal to which the physician may aspire, at times being largely withheld from the proud and yet not fully attainable even by the most humble, one can still be thankful that its quest adds zest to the daily work and often keeps old minds young. If it is difficult of achievement in its application to the concrete problem of the individual patient, how much more difficult is the task of teaching the student how he in his turn may go more directly toward the ultimate ideal.

ELECTROENCEPHALOGRAPHIC STUDIES OF THE ENCEPHALOPATHIES

III. Serial Studies in Measles Encephalitis

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ALTHOUGH the incidence of encephalitis complicating measles is reported to approximate 0.4%,[1] the clinical picture is not a clear one.* Most authors indicate that encephalitis may be suspected if any of the following signs or symptoms appear during the course of rubeola: alterations in the sensorium, including delirium, stupor, or coma, meningeal irritation, focal neurologic signs, and spinal fluid pleocytosis.† Convulsions occur in nearly one-third of the reported cases.‡ Morbidity, mortality, and sequelae vary and apparently are independent of the severity of the measles. The postencephalitic complications may include attention defects, easy intellectual fatigue, impaired learning ability, and restlessness.[3]

Because of the variability of the clinical picture and the difficulty in its recognition, an electroencephalographic study was undertaken in an attempt to aid in the early diagnosis of measles encephalopathy and to evaluate the resultant complications. Particular attention was paid to the findings during the acute stage of the illness in order to learn what clues this technique might offer.

The nonspecific responses of the cortex to injury, from an electroencephalographic standpoint, is the appearance of delta (slow) activity. This principle is true, regardless whether the injury be spontaneous or due to external trauma.[4] The slow waves will usually persist as long as the clinical symptoms and signs are present and usually parallel recovery. Elsewhere, it has been shown that in any form of meningoencephalitis the presence and duration of the delta activity may be good indicators of the existence of cerebral complications § As a corollary, it may be stated that the absence of this delta frequency would rule out the presence of an active encephalopathy.

However, other conditions, particularly convulsive phenomena, may cloud the electroencephalographic picture. After a seizure due to any cause, the record is usually slow, and this slowness may persist for minutes to days. Furthermore, treatment of seizures, especially episodes of status epilepticus, which require the use of large doses of sedative drugs, may further prolong the duration of the slow

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* Neal,[1] p. 82.

† Neal,[1] p. 83, and Reference 2.

‡ Neal,[1] p. 83.

§ References 2 and 5-10.

waves. Since 44 to 88% of measles encephalopathy is complicated by convulsions and/or coma,[11] the interpretation of the delta activity in the electroencephalogram is somewhat more complex than in most of the other forms of encephalitis. This becomes particularly significant when one considers that the entire course of measles encephalitis may not endure for more than 3 to 10 days.

MATERIALS AND METHODS

The records of 10 children with measles encephalitis during the four-year period 1948 to 1952 were reviewed. All patients became lethargic or delirious or had convulsions within 1 to 13 days after the onset of the rash (average, 4.5 days).

The cerebrospinal fluid examinations were done as soon as encephalitis was suspected.

Only those cases are reported that had electroencephalograms during the acute stage of the illness. A total of 48 electroencephalograms was made. Seven patients had records within the first five days of the onset of the encephalopathy, while the other three were done on the 7th, 12th, and 13th days respectively. Repeated (serial) electroencephalograms were made in seven

Summary of Clinical Data and Electroencephalographic Findings in Measles Encephalitis

Case No.	Age at Time of Encephalopathy, Yr.	Severity of Acute Illness	C. S. F.		Convulsions at Onset	Seizures Prior to Encephalopathy	Initial EEG ‡	Follow-Up EEG, Dysrhythmia	Durat. Enceph. at Time of 1st EEG, Days	Follow-Up Period, Yr.	Development §
			WBC *	T.P.†							
1	11	++	138	63	0	+	S_3	+	2	4	N
2	7	++++	298	94	+	0	S_3	++	1	4	N
3	4	++++	180	180	+	0	S_3	++	5	4	D
4	12	++++	0	14	?	0	S_3	+	1	5 mos.	N
5	5	++	64	70	+	?	S_3	+	1	4	N
6	4	++++	50	81	+	0	S_2	++	13	3	N
7	8	++	180	42	+	0	S_2	++	12	3	N
8	7	++++	52	41	0	0	S_1	++	5	3	N
9	6	++	3	Pandy+	0	0	S_1	+++	7	4	D
10	7	++	128	80	0	+	S_1	++	2	4	N

* WBC indicates leucocytes/cu. mm.
† T.P. indicates total protein, mg./100 cc.
‡ S_1, S_2, and S_3 indicate increasing depth of delta activity.
§ N indicates normal development; D, deficient mental growth.

instances up to the 39th day. Six of this latter group have been subsequently followed for periods up to four years, and one has been followed for five months. The remaining three patients were examined once during the acute illness and again three to four years later.

RESULTS

A. Clinical Findings.—The Table summarizes the 10 cases in the series. Three of the five severely ill patients had the seizures in the acute phase. The average duration of critical illness was 4.8 days in the group who had convulsions, as compared with 6.6 days in those who did not. Hence, seizures did not affect the duration of morbidity significantly. Eight had pleocytosis and elevated protein content in the cerebrospinal fluid. There appeared to be no correlation between the severity of the illness and the presence of cells and elevated protein.

Two patients were found to be mentally retarded at the four-year follow-up examination. Case 9 has two epileptic siblings, one of whom is defective. It is not certain whether the present status of this patient is a result of measles encephalopathy or whether she was defective prior to her illness.

B. Electroencephalographic Findings.—The initial electroencephalograms taken during the acute phase of the encephalopathy were slow in all 10 cases. This delta activity persisted for a longer time in those children who had seizures (Fig. 7). In this group, clinical recovery preceded the evanesence of the delta waves, whereas in those without seizures recovery paralleled the electroencephalographic changes.

Of the cases followed for three to four years, there was a persistent dysrhythmia which was mild in two, moderate in six, and severe in one instance. In the 10th

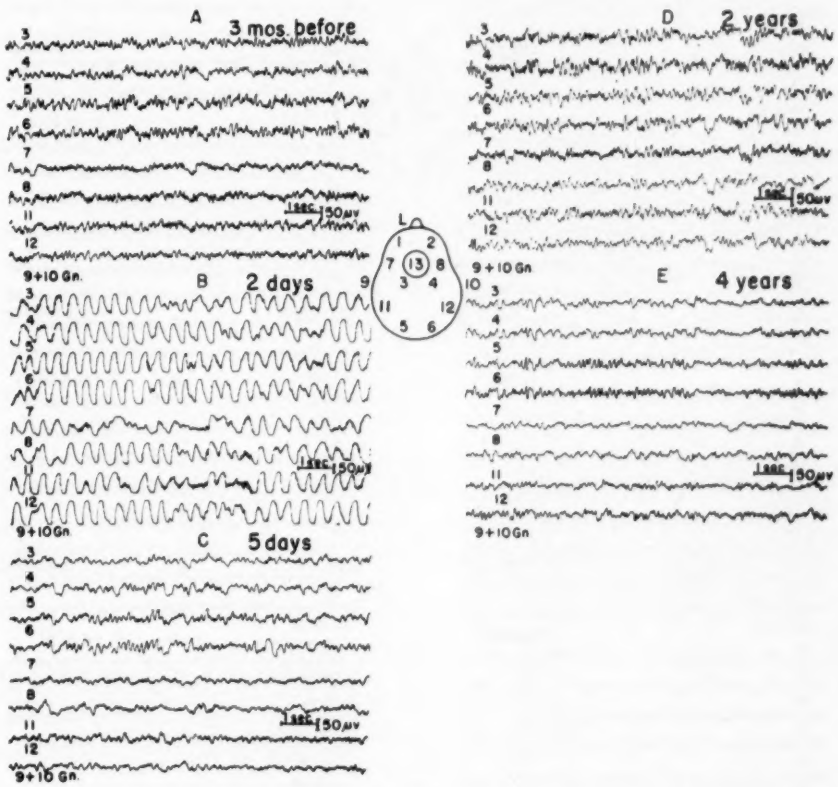

Fig. 1.—Serial studies of an epileptic who developed measles encephalitis. *A*, a control electroencephalogram, three months prior to the illness, is dysrhythmic. *B*, two days after the onset of encephalitic symptoms, the record is diffusely slow. *C*, the delta activity resolved within five days. *D* and *E*, delta activity replaced by the original dysrhythmia, which persisted.

patient, followed only for five months after the acute illness, there was a mildly abnormal record. Six cases demonstrated focal electroencephalographic disturbances, including spikes and slow wave and slow spike discharges. Of the two patients who are defective in their mental growth, there is a mild dysrhythmia in one and a severe dysrhythmia in the other.

To illustrate the difficulty in evaluating both the clinical and electroencephalographic picture and in correlating them, the following protocols are presented.

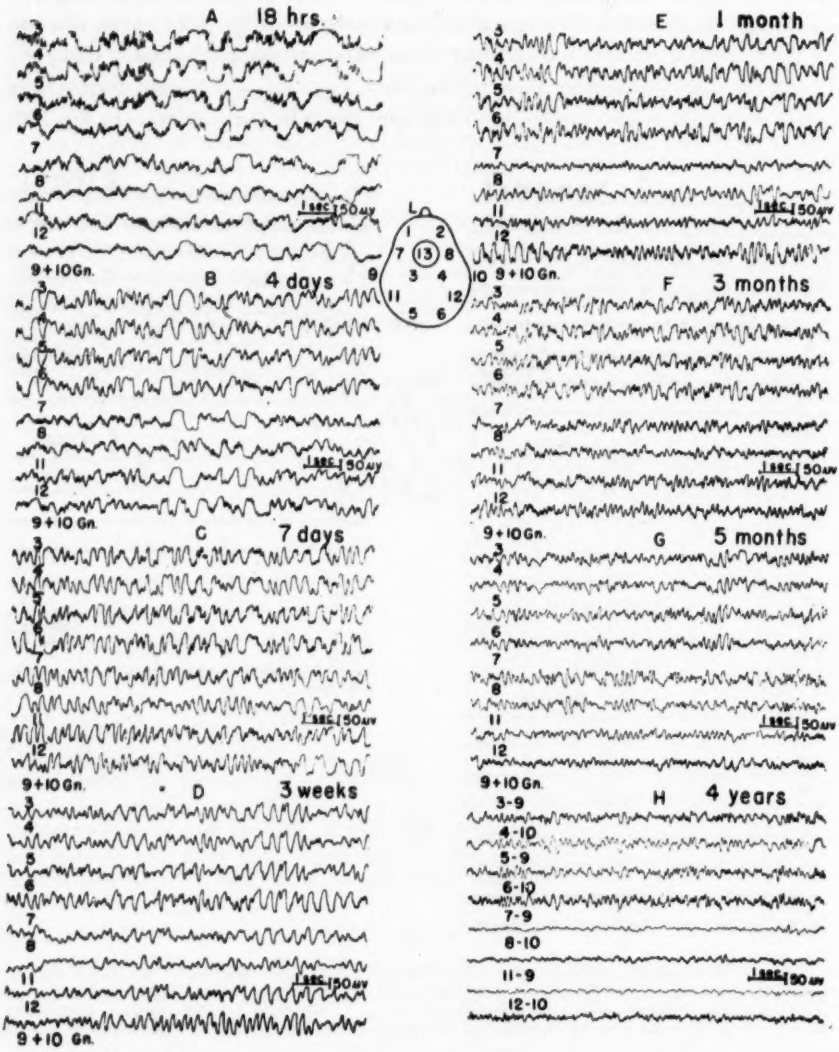

Fig. 2.—Convulsions prolong the regression of delta activity beyond the point of clinical recovery. Serial records of a 7-year-old boy show slow activity gradually resolving over a three-week period after the onset of encephalitis complicated by status epilepticus (*A*, *B*, *C*, and *D*). The electroencephalogram then became dysrhythmic and remained so (*E*, *F*, *G*, and *H*). The patient's mental growth has been normal.

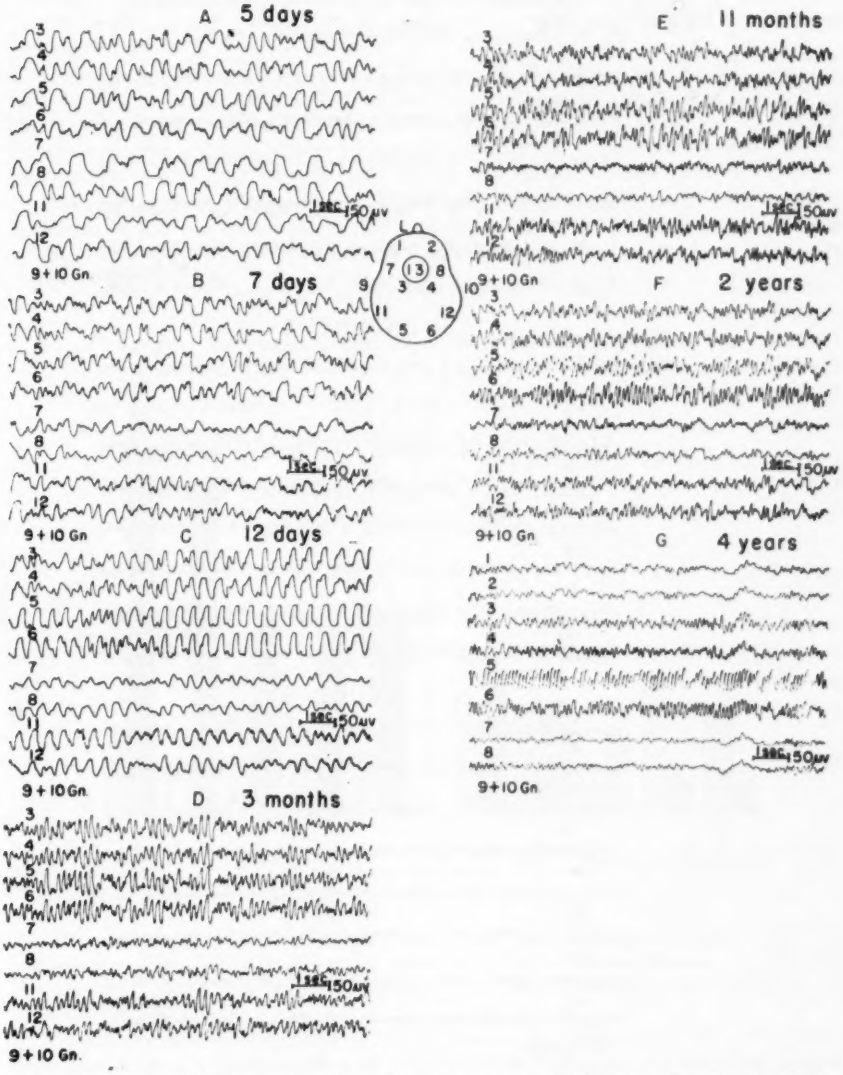

Fig. 3.—The initial electroencephalographic findings may not give clues toward the ultimate prognosis. *A*, *B*, and *C* show slow activity in the records of a 4-year-old girl up to 12 days after the onset of encephalitis. A decreasingly severe dysrhythmia is seen in the next four years, *D*, *E*, *F*, and *G*. However, she is retarded and is a behavior problem.

FIGURE 4

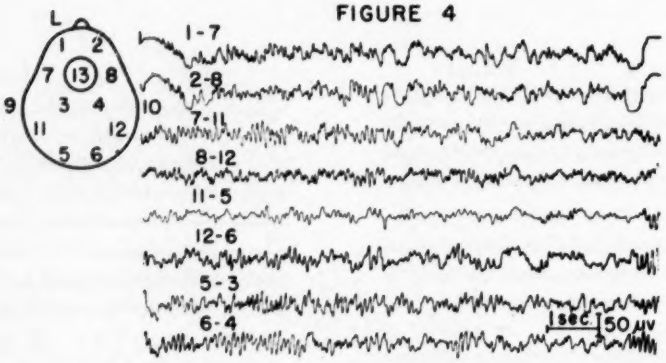

FIGURE 5

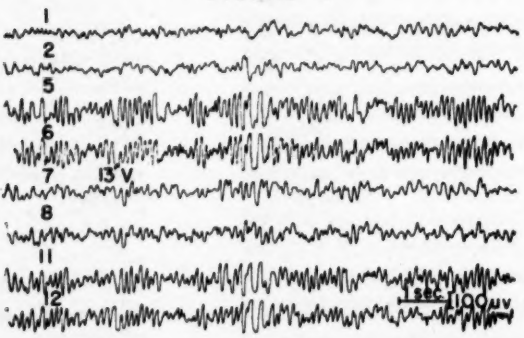

FIGURE 6

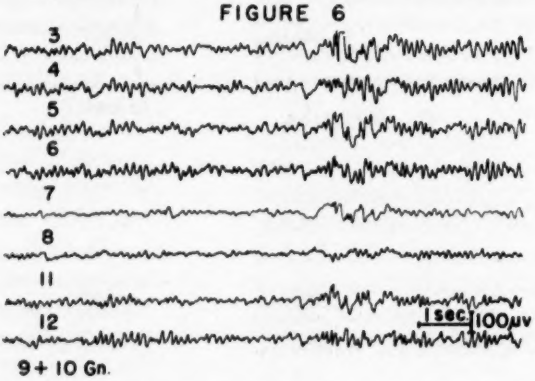

Fig. 4.—A mildly dysrhythmic electroencephalogram of an 11-year-old girl five months after encephalitis. The patient is asymptomatic.

Fig. 5.—A more abnormal record of an asymptomatic 9-year-old girl, three years after encephalitis. The electroencephalogram shows severe diffuse dysrhythmia.

Fig. 6.—The four-year follow-up record of a mentally defective 9-year-old girl, with moderate focal electroencephalographic abnormalities. One sibling is also mentally defective and another sibling is epileptic.

REPORT OF CASES

CASE 1.—T. W., was an 11-year-old boy who had sustained a skull fracture at the age of 18 months. He began to have right-sided focal seizures shortly thereafter. These continued until 1946. On June 11, 1948, he developed a measles rash, which disappeared by June 16. On this latter date, he had a cough and right chest pain and became confused and incontinent of urine and feces.

On admission to the hospital, on June 17, he appeared acutely ill and was lethargic, somnolent, and dehydrated. His temperature was 101.5 F. The conjunctivae were injected, the cervical nodes enlarged, and the tonsils inflamed. There were dullness to percussion, increased breath sounds, and rales at the right base. The neck was moderately stiff. The remainder of the examination, except for the generally hyperactive stretch reflexes, was not remarkable.

During the first two hospital days, he refused food, spoke incoherently, seemed dazed, sleepy, and irritable, and was incontinent. By June 19, he was lucid and cooperative, ate well, and asked to go home. At the time of his discharge from the hospital, on June 24, he was asymptomatic.

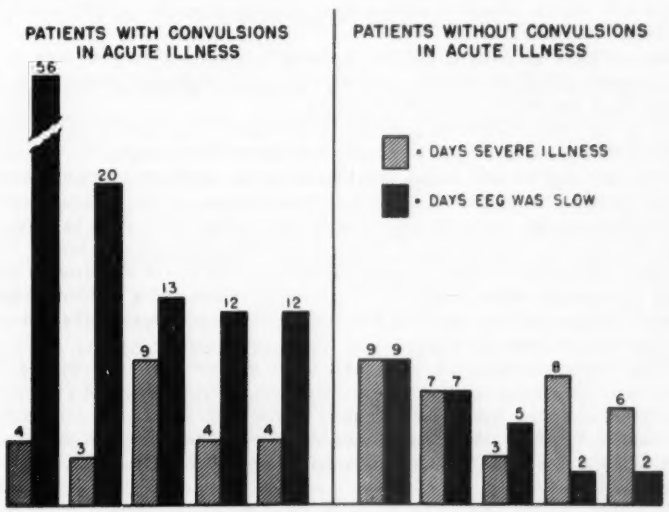

Fig. 7.—A comparison of cases with convulsions as opposed to those without convulsions during acute measles encephalitis. In the seizure group, there is prolongation of slow activity in the electroencephalogram beyond the period of clinical recovery.

The urinalysis, blood cell counts, and x-rays of the chest were within normal limits. The cerebrospinal fluid examination on June 17 showed 138 WBC per cubic millimeter, of which 74% were lymphocytes and 26%, polymorphonuclears. The total protein was 63 mg. per 100 cc. of cerebrospinal fluid.

He was last seen on Sept. 17, 1952. His development has been normal. His school grades have been in the A to B range. He gets along well with his teacher and with other students and has been employed during summer vacations. He is still receiving antiepileptic medication, and the seizures have not recurred.

A control electroencephalogram taken three months prior to the onset of the measles encephalopathy (Fig. 1*A*) was generally dysrhythmic. Two days after the onset of the encephalitic symptoms (Fig. 1*B*), the record showed a marked amount of high-voltage slow activity. Figure 1*C* demonstrates the rapid resolution of the delta waves within five days after the onset of the symptoms. The persistence of the original dysrhythmia, which antedated the encephalopathy, is illustrated in Figure 1*D* and *E*.

This case demonstrates several interesting points. First, it is the only one of the series with a preencephalitis control record. Second, although the child was an epileptic, he had no seizures during or subsequent to his acute illness. Third, the delta activity resolved rapidly within the first five days after the onset of this complication. Last, in spite of his epilepsy, the child has developed normally, and there has been no essential change in his four-year follow-up electroencephalogram over the control.

Case 2.—D. B., a 7-year-old boy, developed headache, photophobia, anorexia, vomiting, malaise, and measles rash on April 17, 1948. These symptoms were continuous and severe until April 20. By April 22, the rash was beginning to fade, and he felt well and was out of bed. However, that evening he had a series of generalized and focal right-sided seizures. He was brought to the hospital immediately and sedated with intravenous amobarbital (Amytal) sodium.

On admission, the rectal temperature was 99 F., the pulse rate 104 and the respirations 24 per minute. He appeared critically ill. There was a diffuse fading macular erythema. The cervical nodes were enlarged. Examination of the heart, lungs, and abdomen revealed no abnormalities. The neck was not stiff. The eyes were deviated to the right, and the right pupil was dilated, but both reacted well to light. He did not respond to verbal commands. Although he withdrew from painful stimuli, he did not move the right extremities. There was an extensor plantar response on the right.

A lumbar puncture on April 22 revealed an initial cerebrospinal fluid pressure of 300 mm. The fluid contained 298 WBC per cubic millimeter, of which 86% were lymphocytes. The total protein was 95 mg. per 100 cc. of cerebrospinal fluid.

In spite of vigorous sedation, he continued to convulse throughout the night of admission. On the morning of April 23, he was comatose. The convulsions ceased during the day, and on the following morning he was awake and able to speak, although he was incoherent. He became lucid on April 25, and steadily improved up to the time of his discharge, on May 1.

He returned to school one week after leaving the hospital. His work has been excellent since then. He was last seen on Aug. 7, 1952, and had the appearance of a healthy 11-year-old boy who spoke well, showed no signs of emotional difficulty, and was of high average intelligence. Neurologic examination revealed only increased stretch reflexes and a positive Strümpell sign on the right. He has not been on a regimen of antiepileptic medication. There is no history of seizures prior to or since his illness.

The initial electroencephalogram (Fig. 2*A*), taken 18 hours after the onset of symptoms, is diffusely slow, but has been modified by the effect of amobarbital sodium. A gradual resolution of slow activity took place within the next three weeks (Fig. 2*B*, *C*, and *D*). However, the records became dysrhythmic, and the abnormalities have persisted (Fig. 2*E*, *F*, *G*, and *H*).

In this instance, it is noted that the slow activity remained for at least one month, although the encephalopathy was severe for only three days. Resolution of the delta activity lagged far behind the clinical improvement. This might be attributed to the seizures which occurred at the onset of his disease. The postencephalitic records are dysrhythmic, even after four years. Yet, during this interval, the patient has developed normally and has been free from seizures.

Case 3.—D. H., a 4-year-old girl, was seen in the outpatient service on Jan. 4, 1949, because of sore throat, hacking cough, and a rash. The symptoms had been present five days. On Jan. 5, the rash began to fade, but the temperature rose to 105 F. and she became delirious. Fever and delirium continued until Jan. 8, when she had a left-sided focal seizure and was brought to the hospital in coma.

On examination, her eyes were deviated to the right. All four extremities showed little resistance to passive manipulations, and there was no response to painful stimuli. All stretch and plantar reflexes were absent. Her neck was not stiff. Examination of the heart, lungs, and abdomen revealed no abnormalities.

Within eight hours after admission, she began to respond to stimulation but was irritable, restless, and confused. On Jan. 9, she was able to answer simple questions. Improvement was rapid, so that by Jan. 11 there were no abnormal signs and she appeared well. She was discharged from the hospital on Jan. 20.

The cerebrospinal fluid examination on Jan. 8, 1949, showed an initial pressure of 190 mm. There were 180 lymphocytes per cubic millimeter, and the total protein was 180 mg. per 100 cc. of cerebrospinal fluid.

After her discharge from the hospital, she slept poorly, was restless, and cried readily. Her hyperactivity was a marked change from her previous behavior. She seemed incapable of maintaining attention on any task for more than a few minutes. She mingled poorly with other children. Within a month after discharge from the hospital, she began to have episodes during which she would run continuously until exhausted. She began to have rapid changes of mood, with sudden rages when deprived of immediate desires. Her behavior became impulsive and destructive. When last seen, on Sept. 4, 1952, she had become more docile, and the running episodes [12] and extreme hyperactivity no longer occurred. Now, at the age of 8 years, she is mentally obtunded and attends a school for retarded children.

Figure 3*A*, taken five days after the onset of delirium, demonstrates a diffusely slow record. Within the next 48 hours, the electroencephalogram began to return to the normal frequency and the patient was markedly improved (Fig. 3*B*). Slow activity was still present 12 days after the initial symptoms (Fig. 3*C*). A decreasingly severe dysrhythmia was noted during the ensuing four-year period (Fig. 3*D*, *E*, *F*, and *G*).

In this case, slow activity was replaced by a dysrhythmia within three months of onset. The acute illness was similar in severity and duration to that in Case 2. The follow-up electroencephalogram, taken after four years, was less dysrhythmic than that of the preceding patient. Yet, this girl has had seizures, is retarded, and is a behavior problem.

COMMENT

Cases 2 and 3 have been presented for comparison. Neither child had seizures prior to the measles encephalitis. Initially, both were in status epilepticus and were critically ill for similar periods of time. Case 2 has since been asymptomatic. The electroencephalogram remained somewhat slow for at least three weeks after the onset. His electroencephalogram after four years is still dysrhythmic, with focal abnormality. Case 3 has become a behavior problem and is mentally retarded. The slow activity in the electroencephalogram had cleared up by the third month. Yet, the record after four years is less dysrhythmic than that seen in the other case.

The correlation, or lack of it, between the ultimate prognosis and the electroencephalogram is demonstrated in three additional long-term follow-up records (Figs. 4, 5, and 6).

SUMMARY AND CONCLUSIONS

The clinical and electroencephalographic findings are reported in 10 cases of measles encephalitis. The recognition of this complication may be difficult when seizures represent the initial manifestation of the disease. The presence of slow waves in the electroencephalogram seems to be indicative of either an acute encephalitis or convulsions in close time-relationship to the tracing. However, the absence of delta activity militates against the diagnosis of active measles encephalitis.

Serial electroencephalograms taken during the acute phase of the illness demonstrate a parallelism between the delta activity and the severity of the disease. The slow waves disappear with resolution of the acute illness uncomplicated by convulsions. However, seizures seem to delay this electrical change.

There appears to be no correlation between the degree and duration of the delta activity and the ultimate prognosis. Likewise, the severity of the final dysrhythmia bears no relationship to the degree of aberration in the mental or behavioral status of the patients studied.

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ACUTE INFECTIOUS LYMPHOCYTOSIS

Report of an Outbreak

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IN THE YEAR 1941, Smith [1] described an entity called acute infectious lymphocytosis, or, as it is widely referred to in the foreign literature, Carl Smith's disease. It is a benign disease of unknown etiology, occurring ubiquitously in a sporadic and epidemic fashion. A tabulation of reported cases has resulted in the designation of four major groupings of the disease: (1) asymptomatic; (2) gastrointestinal (diarrhea, vomiting, and acute abdominal conditions); (3) respiratory, and (4) central nervous system (meningoencephalitic).

The purpose of this paper is threefold; first, to report a carefully observed case of acute infectious lymphocytosis; second, to present a study of an outbreak of this clearly defined disease; and, third, to review the salient features of the disease so that one can easily distinguish it from other more serious illnesses.

REPORT OF CASE

F. C., a 3-year-old white boy, was admitted to the Kings County Hospital on Jan. 20, 1952, from the Convent of the Sisters of Mercy Home because of a generalized convulsion and stupor.

The patient was well until one week prior to admission, when he developed a mild upper respiratory infection. One day prior to admission, the home physician found him in good health.

On the morning of admission, it was noted that he walked stiffly on a wide base and that his eyes were occasionally crossed. The child subsequently had two generalized convulsions, each lasting 3 to 4 minutes.

No history of trauma or drug or lead ingestion was noted.

The birth history was unremarkable.

Physical examination on admission revealed a well-developed well-nourished boy in a comatose state. The temperature was normal, the pulse rate, 125 per minute, respirations, regular, 22 per minute, and the blood pressure, 85/50. No skin rashes or petechiae were noted.

Examination of the head revealed no evidence of trauma. The neurological examination was negative, except for a positive Babinski, bilaterally. Except for a mild degree of dehydration, the rest of the physical examination was unremarkable.

The hospital laboratory studies (Table 1) were all within normal limits, except for an increased excretion of lead in the urine (normal, 0.02 to 0.08 mg. per liter). However, repeated blood lead levels, performed by the Toxicology Section of the New York City Department of Health, were within normal range (0.06 mg. per 100 cc., upper limits of normal).

From the Department of Pediatrics, Kings County Hospital, University Division.

Roentgenographic studies of the chest and skull were negative. The distal metaphyseal ends of the long bones showed a band of ossification condensation or osteosclerosis suggestive of heavy-metal poisoning.

Hospital Course.—The child recovered from the postictal state within an hour after admission. Although the drowsiness and somnolence persisted through the second hospital day, he showed no further evidence of any neurological abnormality while in the hospital.

On the 10th hospital day, a follow-up blood cell count revealed a marked lymphocytic leucocytosis. At this time, a diagnosis of encephalopathy associated with acute infectious lymphocytosis was considered.

During the following six weeks, the patient was observed with periodic blood cell counts (Fig. 1) and a bone marrow examination. The bone marrow was normal, except for an increased number of lymphocytes.

TABLE 1.—*Laboratory Studies of Patient F. C., Aged Three Years*

Tests	Day					
	1/20	1/21	1/26	1/31	2/3	2/7
Blood						
Urea, mg./100 cc.	50	36	..	..	..	..
Sugar, mg./100 cc.	92	95	..	..	..	..
Calcium, mg./100 cc.	10.0	..	..	..	..	..
Phosphorus, mg./100 cc.	3.5	..	..	..	..	..
CO_2, vol. %	36	..	..	..	..	..
Lead, mg./100 cc.	..	..	..	..	..	0.02
Mazzini	Negative	..	..	..	..	..
Culture	Negative	Negative	..	..	..	..
Heterophile						
Nonabsorbed	..	Negative	..	..	Negative	..
Absorbed	..	Negative	..	..	Negative	..
Urine						
Analysis	Normal	..	Normal	..	..	Normal
Lead, mg./L.	..	..	..	0.39	..	0.24
Spinal fluid						
Color	Colorless	Colorless	Colorless	..	..	..
Character	Clear	Clear	Clear	..	..	..
Cells	0	0	0	..	..	..
Protein	27	27	23	..	..	..
Chlorides	700	660	748	..	..	..
Sugar	40	71	58	..	..	..
Culture	Negative	Negative	Negative	..	..	..

The child was completely asymptomatic throughout the entire course of the disease.

On the 43d hospital day, the child developed rubeola and was sent to Kingston Avenue Hospital. He was subsequently discharged to the home.

Several weeks later, he was readmitted because of a second afebrile seizure.

A general work-up, including urinalysis, spinal tap and blood chemistries, was again negative. White blood cell counts were less than 10,000, with normal differentials. An electroencephalogram done on April 10, 1952, revealed a pattern differing not too much from the first electroencephalogram on Jan. 29, 1952. There was nothing to indicate abnormal features; no focalization, lateralization, or burst formations. A pneumoencephalogram was normal.

During the past year he has had a third afebrile seizure. Initially, we had considered lead as the most likely offending agent because of the urinary blood level and long-bone roentgenograms. However, simultaneous studies of controls revealed inordinately high urinary lead levels. In view of the absence of acetone, sugar, or increased calcium in the urine in addition to normal blood levels and spinal fluid chemistries, we did not feel justified in attributing the convulsive onset to lead poisoning. In retrospect, we are obliged to conclude that the initial seizure was the first manifestation of idiopathic epilepsy, rather than the meningoencephalitic forms of infectious lymphocytosis.

STUDY OF THE OUTBREAK

Site and Institution Population.—The Convent of the Sisters of Mercy is located in the center of Brooklyn. During the period of investigation, it was accommodating 107 boys (age range from 2 to 6 years), 41 girls (age range from 10 to 15 years), and 13 adults. Sixty boys (age range from 2 to 4 years) slept in Dormitory "A." The remaining 47 boys slept in Dormitory "B."

Discovery of the Outbreak.—After the diagnosis of infectious lymphocytosis was made on patient F. C., field trips were made to the home to investigate the possibility of an outbreak being present. Between Feb. 8, 1952, and March 20, 1952, the home was visited five times. During the first week of the study, white blood cell counts and blood smears were taken from the entire home population. The 60 children in Dormitory "A," where patient F. C. slept, had a WBC and a blood smear repeated three times during the first 21 days of the study. The remaining children had their blood cell counts repeated only if their initial WBC was > 10,000 per cubic millimeter. As a result of these studies, nine other children had findings

TABLE 2.—*Hematologic Data from Cases with Acute Infectious Lymphocytosis*

		Day																			
		2/8		2/12		2/15		2/19		2/25		2/27		3/3		3/6		3/20	
Case No.	Age, Yr.	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %	WBC/ Cu. Mm.	L., %
1	2½	64,300	96	78,300	..	80,100	68	45,400	78	.....	..	23,500	52	15,000	..	8,700	48	6,800	34
8	5	25,600	83	38,100	88	22,600	90	24,000	91	14,000	50	.....	..	16,100	42	16,000	..	8,500	43
19	3	82,400	85	74,000	80	46,000	..	18,600	59	.....	..	20,000	65	14,800	..	.....	..	11,000	45
20	2	76,800	94	63,000	86	24,800	64	19,800	74	20,000	..	18,800	76	15,300	..	14,700	51	7,500	..
27	3	86,000	93	94,200	85	47,400	72	22,000	68	22,000	66	.....	..	21,300	..	.....	..	19,400	53
28	2½	33,300	90	37,300	87	80,400	88	96,000	94	90,000	85	.....	..	23,500	..	15,000	43	8,700	55
36	3	17,600	45	.....	..	.....	..	.....	..	40,500	..	67,000	90	93,000	94	99,000	92	41,800	80
55	2½	95,000	80	84,400	84	122,000	86	92,000	86	38,500	76	.....	..	14,300	50	10,400	..	12,800	43
74	6	.....	..	63,400	78	59,300	84	58,200	96	.....	..	37,500	81	32,800	..	32,000	59	10,000	47

compatible with acute infectious lymphocytosis. These were considered on the basis of a leucocytosis due to an increase of normal or small lymphocytes, lasting more than 14 days.

Seven other cases were thought to be in the recovery phase of the disease on the basis of one or more WBC > 15,000 per cubic millimeter, with > 50% lymphocytes, not lasting 14 days, but having > 500 eosinophiles per cubic millimeter.

All nine of the acute cases were admitted to the Kings County Hospital for observation and study.

History.—Prior to admission, all of the children had mild upper respiratory infections.

Physical Examination.—The examination of the entire group was negative, except for one child, who had herpes labialis. No lymphadenopathy, hepatomegaly, or splenomegaly were noted in any of the children.

Hospital Course.—Several days after admission, a mild but foul-smelling diarrhea was noted in seven cases. It responded readily to general supportive and symptomatic treatment and gradually disappeared in 48 to 72 hours. These children's temperatures never exceeded 99.5 F.

The typically benign nature of the disease was apparent throughout the entire period of observation. The children's appetites, sleep habits, and behavior were undisturbed.

Laboratory Findings.—Blood cell counts were repeated frequently in the hospital (Table 2).

The hemoglobin in all cases remained within normal limits throughout the entire course of the disease. The sedimentation rates (Wintrobe) were all normal. The highest WBC was 122,000 per cubic millimeter. Six cases had a peak WBC > 80,000 per cubic millimeter, three cases had a peak > 60,000, and one had a

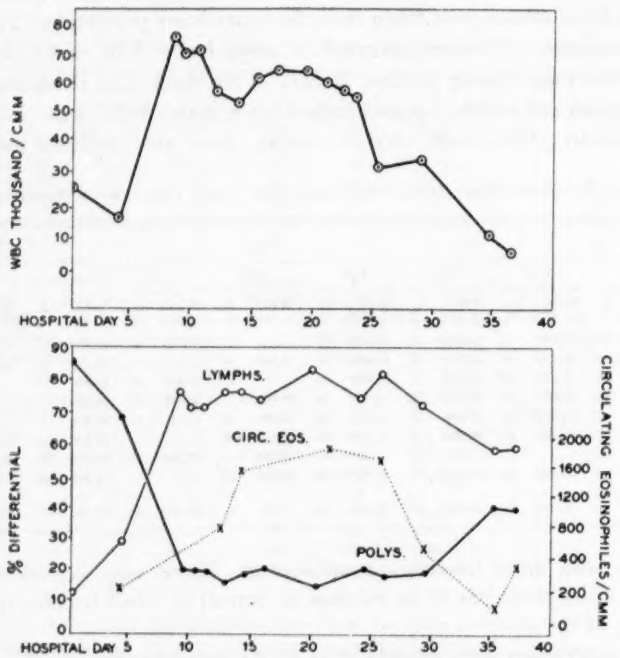

Fig. 1.—Patient F. C., aged 3 years, with acute infectious lymphocytosis, showing WBC, differential, and eosinophiles.

peak of 38,000. Lymphocyte peaks ranged between 85 and 96% in the active cases. The course of the leucocytosis coincided almost identically in all cases (Fig. 1 and Table 2). The average duration of the leucocytosis was approximately 30 days.

Sternal bone marrow aspirations were performed on six of the nine hospitalized cases between Feb. 21, 1952, and Feb. 25, 1952 (Table 3). There was a notable increase in the number of lymphocytes and a slight increase in the eosinophilic series. The other bone marrow elements were not remarkable.

The following blood studies were all found to be within normal limits: urea, sugar, Mazzini, cephalin flocculation, thymol turbidity, cold agglutinins, and heterophile (absorbed and nonabsorbed). Viral antibody studies were done by the New

York City Department of Health. They included tests for mumps, lymphocytic choriomeningitis, Eastern and Western equine encephalitis, St. Louis encephalitis, Japanese B encephalitis, and psittacosis.

Five weeks after admission to the Kings County Hospital, there was an outbreak of rubeola on the children's ward. Six cases were affected. The remaining three cases received prophylactic doses of gamma globulin. The course of the rubeola was uncomplicated in each case. It was observed that the onset of the measles had a definite modifying effect on the natural course of the leucocytosis. No rebound elevations were noted after the termination of the measles outbreak.

All the children were subsequently returned to the institution. In a 12-month follow-up study, all of the children except patient F. C. were found to be clinically well and were developing normally.

TABLE 3.—*Bone Marrow Studies*

	Normal Average, %*	Case No.					
		28	36	19	55	20	27
Lymphocytes, %	10	62.0	51.7	55.0	64.5	60.7	54.5
Eosinophilic series, %	3.5	3.0	5.2	7.4	5.4	7.7	2.2
Other WBC series, %	64.5	35.0	43.1	47.6	30.1	41.6	43.3

* According to Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951, p. 50.

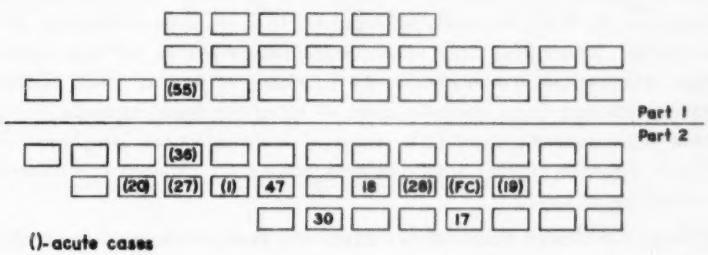

Fig. 2.—Bed plan in Dormitory "A," with locations of children with infectious lymphocytosis.

Experimental Investigation.—Specimens of nose and throat washings, blood, bone marrow, feces, and spinal fluid were submitted to Dr. W. Schlesinger * and Dr. H. Hodes.† Though some studies have been made, no conclusive data have yet come from these investigations.

Because infectious lymphocytosis is a relatively benign disease, repeated blood cell counts over a period of at least four months would be necessary to find all cases in an epidemic. This was not technically feasible, and, therefore, our evaluation and comments on the epidemiology, incubation period, and clinical features of the disease are necessarily limited.

Eight of the 10 acute cases and 4 of the 7 recovery cases were found in Dormitory "A." These children were clearly grouped to one side of the dormitory

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† Pediatric Research Laboratory, Mount Sinai Hospital, New York.

(Fig. 2). In Dormitory "B," four out of five acute and recovery cases were also found in very close proximity to one another. These findings are suggestive of the high infectivity of the disease.

Interdormitory activities were limited to mealtimes. During these periods, however, the groups were clearly segregated. Dormitory "A" was divided into two parts, each having its own teacher, bath, washroom, and toilet. Both sections slept in one large room and also mingled freely in the same play areas. Though these facts may help to explain the greater number of cases in one part of Dormitory "A," we feel that other factors, such as past infection, individual susceptibility, and amount and virulence of the infecting organism must be considered.

Removing the acute cases to the hospital perhaps caused the outbreak to terminate prematurely. Blood cell counts repeated on all the remaining children in Dormitory "A" three weeks after admission of the acute cases to the hospital did not reveal a single new case. Because of this, the incubation period of the disease could not be adequately determined.

Except for some doubt remaining with patient F. C., these cases confirmed the benign nature of the disease.

COMMENT

Prior to Smith's contribution, cases had been reported mistakenly as variants of infectious mononucleosis. Thelander and Shaw [2] listed two such cases, with encephalitic and meningitic manifestations. Earlier, Wilson and Cunningham [3] reported a case in a 21-year-old student, with a benign hyperleucocytosis and lymphocytosis. In 1941, Reyersbach [4] reported 16 such cases of atypical infectious mononucleosis, which have been subsequently recognized as the first institutional outbreak of infectious lymphocytosis. In England, as late as 1942, Kilham and Steigman [5] reported three sporadic cases of infectious mononucleosis. Steigman [6] has since recognized the cases to be those of acute infectious lymphocytosis and, in addition, reported another small outbreak among six children in southern England, occurring in 1942.

Etiology.—Although many studies have been undertaken, no definite agent has been incriminated at this time. Attempts to isolate bacteria or virus have been unsuccessful.‡ Complement fixation and antibody studies § have been unrewarding. Trauma [11] has been considered. Stomatitis and herpetic eruptions have occurred in association with infectious lymphocytosis.‖ Positive stool cultures for Giardia lamblia were noted in four of Dunn's [13] cases. The author postulated that acute infectious lymphocytosis should be regarded as a reaction of a host to a variety of agents rather than to a specific entity. However, the appearance of the condition in epidemic form seems to speak against the nonspecificity of the hematologic response and is more in keeping with an infectious origin. The possibility of ectoparasites as a causal agent has not been explored.

Epidemiology.—There have been eight previously reported epidemics; five in this country, two in England, and one in France. Pertinent data concerning the epidemics in this country are summarized in Table 4.

‡ References 4 and 6-8.

§ References 9 and 10.

‖ References 9, 12, and 13.

Five reports of outbreaks among siblings have appeared in the literature. Smith [9] reported three in the same family and a fourth case resulting from a hospital contact. From these patients, a possible incubation period of 12 to 21 days was postulated. Moyer and Fisher [14] reported five cases in Negro siblings aged 2½ to 10 years, with findings of diarrhea and a mild temperature elevation. Klemola and Hamarinen,[15] in Finland, list five cases in siblings, with diarrhea and an eosinophilic count greater than 5% at some time during the disease. Lorenz and co-workers [16] reported two cases affecting brothers in a family of five. Recently, Riley [17] reported two cases in young brothers having respiratory symptoms. The course was not affected by penicillin in one case or by chlortetracycline in the other.

Race and sex seem to be more a function of the particular institution or group exposure, rather than an indication of any special predilection. On the other hand, the disease appears to be predominantly confined to children, although cases occurring in adults have been reported.¶ In the epidemic reported by Barnes and co-workers,[7] 15 of the 87 affected were over 17 years of age.

TABLE 4.—*Reported Epidemics of Infectious Lymphocytosis in the United States*

Author	Year	Institution	Age Range, Yr.	No. of Cases	Range of WBC/Cu. Mm.	Lymphs, % at Peak	Duration, Wk.
Reyersbach [4]	1939-40	Rheumatic Fever Rest Home	6-14	16	18,000-59,500	71-93	1½-6
Finucaine [8]	1942-43	Tuberculosis Sanatorium	1½-5½	21	22,500-120,000	70-97	2½-7
Peterman [12]	1947-48	County Children's Home	Majority under 5	28	18,900-147,000	63-94	Up to 7
Lemon [24]	1949	Children's Home	1½-7	17 19*	>15,100 <15,100	70-94	Up to 12
Barnes [7]	1947	Training School for Mental Defectives	Majority 2-17	87	20,000-77,400	60-93	Up to 7
Scalettar	1952	Children's Home	2-6	10 7*	38,000-122,000 15,800-23,300	85-96	4-5

* Probable cases with abnormal lymphocyte or eosinophilic percentages.

There is no unanimity as to the infectivity of infectious lymphocytosis. Reyersbach [4] implied that her reported epidemic had a low rate of spread. It was sporadic over a six-month period, with an interval of 48 days between the discovery of the first and the second case. The epidemic reported by Peterman and co-workers [12] lasted four and one-half months. Examination of 10 roommates of the first patient failed to reveal any evidence of infection. Other observers # concur on the low infectivity incidence. On the other hand, some reports speak of the high attack rate of infectious lymphocytosis. Barnes and co-workers [7] discovered their first case while doing a routine count on an epileptic child. Investigation revealed three other children in adjoining beds in the same dormitory to have a similar blood picture. A possible explanation may be that some are infected without developing fully characteristic blood pictures or may be in the recovery phase. Thus Lemon and Kaump,[24] in addition to 17 cases having elevated white cell counts and lymphocytic predominance, also reported 19 other cases in which the white cell counts were not elevated, but the lymphocytes and eosinophiles were above normal.

¶ References 3 and 18-21.

References 13, 22, and 23.

Hematology and Histology.—Barnes and co-workers [7] noted the lymph nodes to have moderate hyperplasia and that there was proliferation of the reticulum of the medullary sinusoids; however, the changes were not considered pathognomonic. Results of lymph node biopsies from the cervical and inguinal area in two of Smith's [9] patients demonstrated proliferation of the lining reticuloendothelial cells of the sinuses, as well as areas of hyaline degeneration of many of the germinal centers of the lymph follicles. Meyer [26] felt that the follicles were unusually small and on occasion revealed hyalinization.

Bone marrow findings have been limited to a rise in the lymphoid element. This reflects an increased production and implies a peripheral blood dilution. Late in the course of the disease, eosinophile counts have been raised.

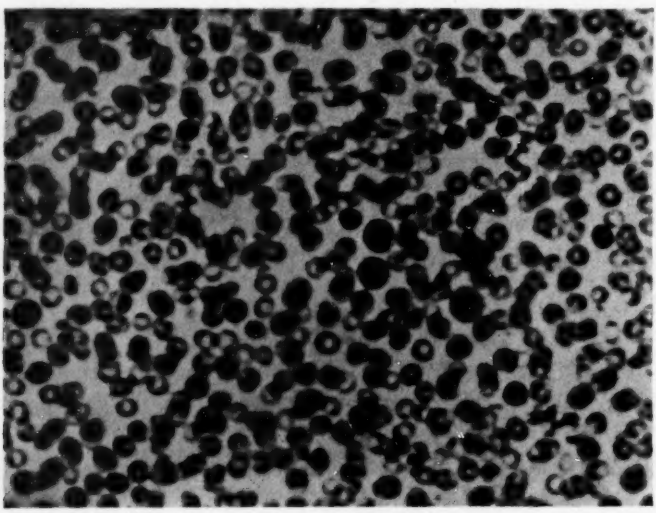

Fig. 3.—Peripheral blood smear of a child with infectious lymphocytosis.

The predominant laboratory finding is a marked leucocytosis with an absolute lymphocytosis. The lymphocytes are considered to be normal and small and to contain the coarse chromatin masses of normal mature cells. Scanty cytoplasm staining a clear blue pale color is more commonly found, although a cell may be moderately basophilic. Only rarely is a larger or intermediate lymphocyte seen. A representative peripheral smear from one of our patients is shown (Fig. 3).

Persistent eosinophilia was first noted by Finucaine. Actually, during the initial phase of leucocytosis (as high as 147,000 per cubic millimeter has been reported), the eosinophile count is low or absent. As the white cell count starts to taper, the eosinophiles may be expected to rise (Table 5).

Nucleated red blood cells were first reported by Barnes.[7] This finding was not observed in our cases.

Clinical Findings.—The majority of the cases reported have been devoid of positive findings. Absence of lymphadenopathy and splenomegaly has been rather characteristic. From epidemic reports, it has become apparent that some cases do

present themselves with signs and symptoms of respiratory infection and gastrointestinal distress, the latter most commonly manifested as diarrhea. Skin involvement, in the form of a mild morbilliform rash, has been reported in a young adult by Duncan.[18] Another report of a maculopapular rash in a young adult has been noted.[20] More recently, Howard [25] reported a case in Chile, in which the child had associated lesions of erythema multiforme.

Of further clinical import has been the appearance of an acute abdomen with this disease. Duncan [27] reported a 5-year-old child with acute abdominal pain having a WBC of 45,000 per cubic millimeter. The pain may be explained on the basis of hyperplasia of the mesenteric lymph nodes.

Differential Diagnosis.—A detailed and complete discussion of the differential diagnosis has been adequately presented by Smith [22] and will not be reviewed here. Briefly, however, there are three diseases which may give rise to an absolute lymphocytosis. They are, pertussis, infectious mononucleosis, and lymphatic leukemia.

The diagnosis of acute infectious lymphocytosis should not be mistaken if one recalls its usual paucity of clinical signs and symptoms and its lack of positive findings. It is true that there are reported exceptions, with gastrointestinal and central nervous system symptomatology. However, clinical appraisal, bacteriological examination, serum antibody studies, and a careful routine hematological work-up (including bone marrow studies) will help to differentiate these diseases.

TABLE 5.—*Probable or Recovery Cases of Infectious Lymphocytosis*

Case No.	Highest WBC/Cu. Mm.	Peak Lymphocytes, %	Peak Eosinophiles/ Cu. Mm.
5	23,300	60	1,860
11	15,800	54	990
12	22,500	47	1,800
17	22,700	56	1,200
18	22,400	42	460
30	18,100	48	720
47	18,000	52	720

SUMMARY

An outbreak of acute infectious lymphocytosis has been described, together with a review of the pertinent literature. Despite the presenting symptomatology, at times involving the respiratory, gastrointestinal, and central nervous system, the benign nature of this disease is stressed.

Dr. Janet Watson, Hematology Department, State University of New York College of Medicine at New York City, Brooklyn, and the adminstration of the Convent of the Sisters of Mercy assisted with this study.

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HYPERTHERMIA DUE TO HYPERSENSITIVITY TO METHANTHELINE BROMIDE (BANTHINE)

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THERAPEUTICS in pediatrics involves not only the problem of reducing the adult dose in proportion to the size of the child, but also the awareness that infants may have peculiar reactions to certain medications that are not at all or rarely encountered in other age groups. Atropine is a well-known example of this; fever may occur from the usual doses, although large doses can be well tolerated by most infants. Naphazoline (Privine) Hydrochloride nose drops is another excellent medication which I [1] and others * have observed to cause sedation and collapse in susceptible infants, while being used in the usual manner as nose drops.

The explanations offered for the mechanisms by which hyperthermia occurs from atropine (Goodman and Gilman [4]) consist of the following: (1) the suppression of perspiration, (2) restlessness, and (3) central effects. Temperatures as high as 107 to 109 F. have been reported in infants after administration of atropine. It is noteworthy that animals which do not perspire, e. g., the dog, show no fever from atropine.

Methantheline bromide (Banthine), or β-diethylaminoethyl xanthene-9-carboxylate methobromide, has been proposed as a substitute for atropine since 1950 and has proved to be very effective.[5] It is a parasympathicolytic agent having the peripheral action of anticholinergic drugs and the ganglionic blocking action of drugs such as tetraethylammonium chloride.[6] Detailed statements are available as to its therapeutic and pharmacological action in a manual by the manufacturers,[6] but no mention is made of the hyperthermic reaction. The literature † also fails to reveal any mention of hyperthermia. The only reference to fever is by Benson,[7] who found two cases of temperature up to 102 F. in infants given methantheline.

In an effort to understand the possible mechanism for fever production from methantheline, a study of the chemical structure comes first. There is a slight similarity between atropine and methantheline in that in both agents the amine group is separated by two carbon atoms from the ester linkage in the side chains; there are similar relations in syntropan and adiphenine hydrochloride (Trasentine). However, it is highly debatable whether this feature of the molecular structure is significant in producing hyperthermia, insofar as the last two compounds (as well as many others containing this grouping) have never caused high fever. On the other hand, Best and Taylor [8] mention such chemically totally dissimilar drugs as β-tetrahydronaphthylamine, ergotoxine, and dinitrophenol as being capable of

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* References 2 and 3.

† References 5-30.

causing fever. The first compound causes fever by cutaneous vasoconstriction, increased muscular activity, and adrenal medullary stimulation. The latter two act on the heat center. One may conclude, therefore, that the explanation for the production of hyperthermia does not lie in chemical configuration alone.

The explanation for the production of fever by methantheline probably lies in its pharmacological similarity to atropine, which acts by the three aforementioned mechanisms. Thus, Rossett and Stephenson [9] state that the toxic psychosis produced in their patient by methantheline was similar to that caused by atropine when it had been given to him previously.

One other factor remains to be discussed, namely, the dosage. This has been carefully studied in a large number of infants and children by Benson, who concluded that "not more than 12.5 mg. every 12 hours" is a proper starting dose for newborn infants. Levy and Zweifler [10] agree, but in using individual doses of 5 mg. and increasing in stepwise quantities, they noted marked flushing with 10 mg. doses of methantheline in two of 50 infants, neither of whom had any difficulty with 5 mg. doses. With atropine, the usual manner of dosage (in pylorospasm, for instance) is to start with a small dose and increase up to the amount at which toxic symptoms are noted. Therefore, one can surmise that most persons would get toxic effects from methantheline or any other medication if the dose were sufficiently increased. However, in addition to the quantitative factor, there is also an important qualitative factor.

Certain persons are so sensitive to some drugs that the usual doses cause reactions seen either with high doses only or reactions with symptoms and signs altogether different from overdosage alone. In other words, an allergy, idiosyncrasy, or hypersensitivity is incriminated. In the case to be presented, however, although there is an allergic family history, the reaction had none of the signs usually associated with atopy, but rather the signs to be expected from poisoning due to overdosage. Benson performed intradermal tests on 415 children with methantheline, as well as 85 conjunctival tests, and concluded that they were of no value in detecting untoward reactions to the drug. It is well known that skin tests are of very little value in revealing drug allergy. As far as dosage is concerned, Benson found that a 4-week-old infant could take 12.5 to 25 mg. of methantheline every six hours without any unusual reaction. A 6-week-old infant was also able to take as much, and developed flushing of the skin and dilatation of the pupils only on a dosage of 50 mg. four times a day. Levy and Zweifler's daily dose in infants was as high as 30 mg., with no serious symptoms. Thus, one can only conclude that the patient to be presented here must have been unusually sensitive to average doses. In view of the fact that this type of reaction to atropine occurs mainly in infants and in cases of cerebral palsy, in which poisoning develops from the small amount of atropine needed to dilate the pupils, it may very well be that the underdeveloped or damaged nervous system is the basis of this sensitivity.

REPORT OF CASE

L. E. A. was a 3½-week-old white boy suffering from recurrent attacks of severe colic. Past history revealed that he had had a spontaneous delivery and had weighed 7 lb. 11 oz. (3,487 gm.) at birth. Circumcision was done on the sixth day without difficulty. His diet had recently been changed from evaporated milk to whole milk because of colic. In the way of medications, he had been able to take the usual doses of acetylsalicylic acid and phenobarbital without ill effect.

Family history was significant in so far as his mother, maternal aunts, and his father have had inhalant allergies, but there was no known drug idiosyncrasy. A sibling has had nephrosis.

The present illness began on Oct. 27, 1953, with the administration of methantheline to alleviate colic. Decision to use this drug was based both on my previous successful experience and on the encouraging report by Levy and Zweifler.[10] The recommended dose of 12.5 mg. (used for newborn infants) was ordered, but, owing to spillage, the infant was given an estimated two-thirds of the powder, or 8 mg., by mouth. Within two hours it was noted that the skin had become very red and the temperature had risen to 105 F. The infant was hospitalized, and examination revealed a temperature of 106.8 F. three hours after the ingestion of methantheline. There was marked generalized flushing of the skin, which was also dry. The heart rate was about 250 per minute, and the respirations were very rapid and accompanied by an expiratory grunt. The pupils were dilated, and the mucous membranes of the mouth were dry. There was severe restlessness.

Immediately upon admission, the stomach was lavaged with water to remove any remaining drug. The patient was then placed in a tub of cold water, with rapid decrease of temperature to normal. The tachycardia and tachypnea gradually subsided over a period of two hours, making it unnecessary to employ either neostigmine or methacholine (Mecholyl) as antidotes. He slept peacefully thereafter and took his formula well. The temperature rose once to 101 F. the next day, but it then returned to normal and stayed there. Excessive thirst persisted for two days. Complete blood studied revealed RBC, 3,000,000; hemoglobin, 13.1 gm. per 100 cc.; WBC, 17,600, with 44% neutrophiles and 54% lymphocytes. Urinalysis gave negative results. Examination one week after the illness did not show abnormalities. The colic, incidentally, was relieved for a few days.

SUMMARY

This case is the first reported hyperthermic reaction to methantheline bromide (Banthine) in an infant. The reaction is probably due to unusual sensitivity to an average dose of the medication. It is similar to the reaction to atropine. The family history of allergies and the age of the patient constitute predisposing factors. If a practical lesson is to be learned from this case, it is that it probably would be best to start with doses of methantheline bromide in infants as low as 5 mg. and then to use 5 mg. increments in an effort to detect sensitive patients before hyperthermic levels are reached.

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GROWTH OF MANDIBLE IN INFANTS WITH MICROGNATHIA

Clinical Implications

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SINCE Pierre Robin first described the syndrome of hypoplasia of the mandible, cleft palate, glossoptosis, inspiratory retraction of the sternum, cyanosis, and malnutrition which has come to bear his name,* numerous reports of cases have appeared in the literature. The fatal termination of some cases is a testimony of the serious nature of the syndrome. Although a variety of mechanical and surgical therapeutic procedures have been suggested,† a rationale for the proper management of individual patients has not been adequately presented. It is the purpose of this communication to present observations from the serial studies of patients with this disorder, upon which a physiologic approach to management may be based.

It is generally agreed that the pathophysiologic events in this syndrome are as follows: the receding chin fails to support the tongue in its normal forward relationship and hence fosters the glossoptosis. The retroposed tongue impinges against the posterior wall of the pharynx, obstructing inspiration and impeding feeding. Slight excesses in mucous or saliva tend to enhance the pharyngeal obstruction and may precipitate severe cyanotic seizures, resulting in death. Starvation and respiratory infections, or both, may follow as a consequence of the chronic glossoptosis.

Since the major symptoms are definitely related to the micrognathia, it was of special interest to focus our attention upon the growth of the mandible in these infants. In reviewing the published case reports, it appeared that two questions, basic to an understanding of a more appropriate management of these cases, remained unanswered. The first question could be phrased as follows: How soon would mandibular growth be sufficient to accommodate the tongue and hence insure a more adequate airway? This is assuming that the infant could be placed in an adequate metabolic climate. The answer to this question would have an important

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* References 1 and 2.

† References 3-10.

bearing on immediate management. The second question is related to whether or not mandibular growth would be sufficiently sustained to provide an esthetically satisfactory facial profile.

The answer to these questions had to await the development of accurate roentgenographic techniques for measuring the growth of the head in infants, which made it possible to undertake a serial study of the growth of the micrognathic mandible. The results of these investigations have provided useful information as a basis for therapy and prognosis.

METHODOLOGY

In 1931, Broadbent [11] introduced cephalometric roentgenography as an accurate means for measuring the growth of the head in man. The instrument used, the Broadbent-Bolton cephalometer, consisted of a firmly based head-positioning device

Fig. 1.—A close-up of the infant in the head-holder. The correctional scale above the baby's face is projected onto each film in order to correct linear enlargement.

and two x-ray tubes in fixed relationship to the head-positioner. This arrangement provided a constant position of the head in relation to the source of x-rays. Thus, it became possible to reproduce the same lateral and posteroanterior views of the head at desired intervals.

The resultant films are placed on a transilluminated tracing table and covered with a sheet of fine tracing paper. A fine hard pencil is employed to trace not only a variety of bony structures but also the outlines of the soft tissue profile, the soft palate, the tongue, and the outline of the pharyngeal airway. Where it is desirable to study the changes incident to growth during a given period of time, one tracing is superimposed upon the other, and the differences can be assessed by angular and linear measurements. During the past 25 years, cephalometric roentgenography has produced valuable information pertaining to the growth of the head in normal [12] and pathologic conditions [13] in man.

In 1949, Oritz and Brodie [14] described a cephalometer specifically designed to study the growth of the head in the newborn infant. Their instrument was built around a table upon which the infant was placed in a supine position. A single x-ray tube was employed to obtain a lateral view of the head. This instrument was redesigned to assure greater precision and to include a second x-ray tube for postero-anterior views (Fig. 1).[15] In order to obtain uniformly accurate results in positioning the infants in the head-holding device, it was generally necessary to sedate these children with an aqueous suspension of a barbiturate given in a retention enema.

The continued reference to certain landmarks employed in cephalometric roentgenography ‡ merits special mention (Fig. 2). The following is a glossary of the terms employed:

1. N—nasion, a point on the suture between the frontal and nasal bones.
2. S—sella turcica; the center of the sella turcica is determined by inspection.
3. S-N—a line connecting Point S and Point N; this line is considered to delineate the anterior portion of the base of the cranium.

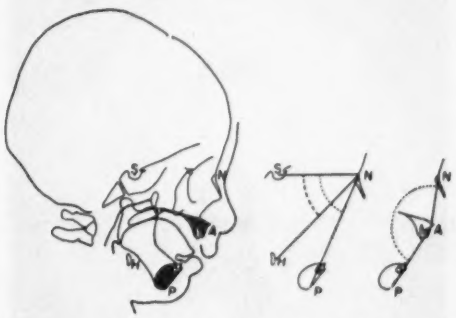

Fig. 2.—A tracing of a lateral film representing the principal landmarks and measurements employed in this investigation.

4. Point A—subspinal, the deepest midline point on the maxilla between the anterior nasal spine and the prosthion.
5. P—pogonion, the most anterior point on the mandible in the midline.
6. Facial plane—a line from the nasion to the pogonion.
7. Facial angle—angle S-N-P; in this report, it is represented as the inside inferior angle formed by the intersection of the line S-N and the facial plane.
8. Angle of convexity—angle N-A-P, formed by the intersection of a line from the nasion to point A, with a line from point A to the pogonion.
9. H—hyoid bone, the most anterior point on the body of the hyoid bone in the midline.
10. Angle S-N-H—formed by the intersection of a line from the sella to the nasion, with a line from the nasion to the hyoid bone.

In addition to the cephalometric roentgenographic measurements, dental impressions of the maxillary arch were obtained at regular intervals. The impressions were cast in dental stone and then subjected to various measurements. The infants were recalled for study every three months during the first year of life and twice annually until the age of 5 years. Thereafter, they were observed annually.

‡ References 12 and 16.

REPORT OF CASES

From a large series of similar cases now under longitudinal study at the Cleft Palate Center of the University of Illinois [15] we have selected three cases for presentation. At birth, each of these infants presented a cleft of the palate and mandibular micrognathia. Despite these similarities, certain important differences existed to vary the management and progress of each infant. The differences to be described in each of these cases represent the major variations which we have encountered in our experience with this syndrome. For the sake of brevity, the case history will be confined to such information as is directly pertinent to the purpose of this paper.

CASE 1.—At 2 months of age, D. R. P., a small white dehydrated baby girl, was admitted to the Research and Educational Hospital, with the principal complaint of intermittent pneumonitis for the previous five weeks. After a normal full-term spontaneous delivery, it was noted

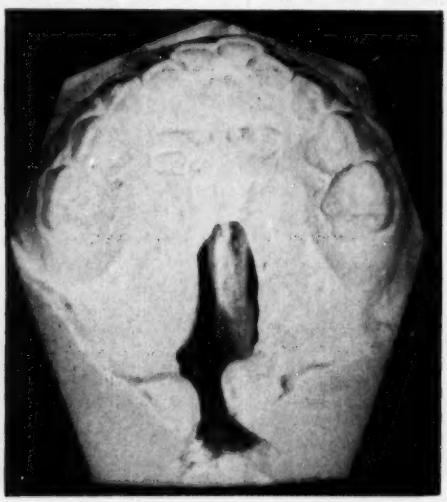

Fig. 3 (Case 1).—A cast of the maxillary arch.

that the baby had a cleft palate and a small mandible. The birth weight was 5 lb. 13 oz, (2,640 gm.). Feeding had been difficult because of the tendency of the baby's tongue to fall back into the pharynx. There was no history of a cleft on either side of the family. The mother gave no history of being exposed to a contagious disease or other illness during her first trimester of pregnancy.

Because of the patient's congenital defects, she presented primarily a feeding problem. An attempt was made to design an obturator so that the baby could be bottle-fed. This was met with failure, and gastric gavage was necessary. However, the patient did not gain weight and continued to do poorly. Approximately one month after admission, it was considered that a tracheotomy was the only procedure which might possibly save the baby's life. After the tracheotomy, respiration was greatly facilitated, and soon the patient was removed from the oxygen tent. Her improvement thereafter was constant. The patient was discharged from the hospital three months after admission, at 5 months of age.

Growth Studies.—Oral examination disclosed a cleft involving the distal margin of the hard palate and extending posteriorly throughout the length of the soft palate (Fig. 3). Ptosis of the tongue was evident.

On the fifth day following the tracheotomy, at the age of 3 months 1 day, the first lateral film was obtained without sedation (Fig. 4). A tracing of this film revealed that the head was in slight dorsiflexion, the position of greatest comfort for the infant. The relative smallness of the mandible and its effect on the facial profile was self-evident. In relation to contiguous anatomical structures, the posture of the tongue was abnormal. It projected through the cleft in the palate into the nasal cavity. In the lateral head plate, the dorsum of the tongue was visible at a level above the palatal plane. Posteriorly, the tongue impinged on the airway. The posterior surface of the tongue, just above the epiglottis, was in close approximation to the posterior outline of the pharyngeal wall. At this level, the airway was almost completely occluded. The tracheotomy tube was in place. Comparison with the illustration in Figure 2

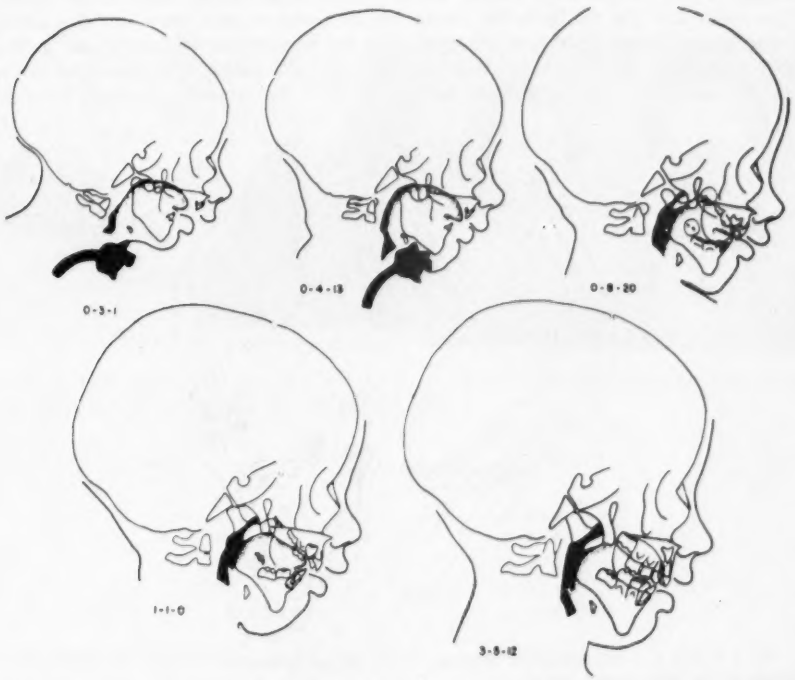

Fig. 4 (Case 1).—A series of tracings of the lateral film from 3 months 1 day of age to 3 years 5 months 12 days. The pharyngeal airway is outlined in dark, and the stippled area denotes the borders of the tongue. A tracheotomy tube is visible in the first two films.

will reveal the configuration of these structures under normal circumstances. The airway in its posteroanterior dimensions is fairly wide, and the tongue occupies a more protrusive relationship to the mandible.

The second film, obtained less than six weeks later, at the age of 4 months 13 days, revealed considerable enlargement of the airway. At the same time, a considerable increment in the growth of the head and, above all, of the mandible was recorded. Subsequent films, up to the age of 3 years 5 months 12 days, give proof of the gradual and continued growth of the lower jaw in relation to the total face and the increase in the dimensions of the pharyngeal airway. At eight months following removal of the tracheotomy tube, the air passage was demonstrated to be quite adequate (Fig. 4).

The superimposed tracings, from 3 months 1 day of age to 3 years 5 months 12 days, reveal the progressive growth of the cranial vault, the maxilla, and the middle face and the increase in length and height of the mandible (Fig. 5). Gradual improvement in the facial

profile was recorded by the changes in the facial angle and in the angle of convexity. The facial angle is a measure of the degree of protrusion or recession of the chin. In this instance, the facial angle increased from 64 degrees, at 3 months of age, to 70 degrees, at the age of 3½ years, indicating a reduction by 6 degrees in the recessiveness of the chin. While the mandible is still in a retrusive relation to the rest of the face, the potential for further improvement with continued growth still exists.

The changes in the angle of convexity were more interesting. This measurement relates the maxilla to the total facial profile. At 3 months of age, the angle of convexity was 140 degrees, and at 3½ years, it measured at 154 degrees. The integrated growth of the several areas of the face was such as to improve the over-all configuration of the facial profile. Serial photographs at 2 months, at 13 months, and at 3 years of age further testify to the changes in this child's face (Fig. 6). In the last photograph, the patient is posed beside her older sibling.

The changes in the position of the hyoid bone are of particular interest, insofar as they reflect a change in the relative position of the tongue. The tongue is composed of several individual muscles originating from the base of the skull, the mandible, the hyoid bone, and

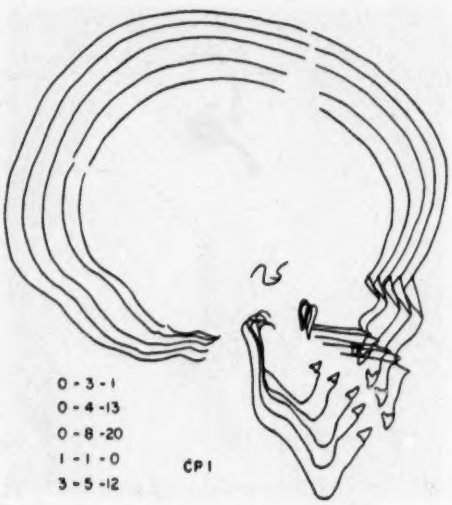

Fig. 5 (Case 1).—Superimposed tracings of the lateral head plate reveals the increments of growth at the various age levels.

the walls of the pharynx. Changes in the position of any of its bony or fibrous attachments would tend to reflect on the position of the tongue. Conversely, changes in the posture of the tongue would reflect on the spatial relations of the mandible and hyoid bone. Therefore, to study the position of the hyoid bone is, in a sense, to study the position of the tongue. With growth there occurs a forward and downward migration of the hyoid bone from the base of the skull. The pattern of changes in the posture of the hyoid bone observed in this patient sheds further light on the favorable adjustments consequent to growth. During the first five months of our studies, the hyoid bone migrated downward and forward. This resulted in an increase in the angle S-N-H. But, from eight months onward, this angle became fairly stable and the hyoid bone began to descend principally in a downward direction (Fig. 7).

Comment.—This case was selected to typify the findings in several similar cases, one of which has been followed to the age of 7 years. Not all cases of Pierre Robin syndrome present such acute histories. When clinical evaluation suggests that no improvement or possibly death may ensue, tracheotomy should be undertaken with-

out hesitation to prevent further aggravation of the symptoms. Once an adequate respiratory exchange was made possible, improvement in oxygenation and feeding followed. In such instances, we have recorded rapid growth of the mandible and concomitant enlargement of the airway. As growth continued, favorable changes in the facial appearance were recorded.

In retrospect, had tracheotomy been resorted to earlier in the management of this patient, some of the concurrent infections might have been averted.

CASE 2.—J. G., a white girl, was referred to the outpatient clinic of the Cleft Palate Center at the age of 2 months, with a diagnosis of cleft palate and mandibular micrognathia. Following

Fig. 6 (Case 1).—On the left, at 2 months of age, in the center, at 13 months, and, at the right, at 3 years of age, posed beside her older sibling.

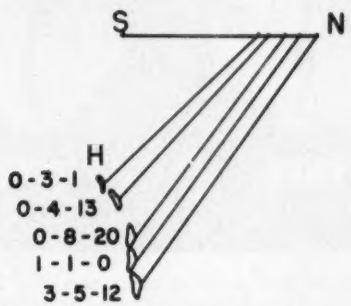

Fig. 7 (Case 1).—The changes in the posture of the hyoid bone as related to the anterior cranial base.

an uneventful pregnancy, the delivery was normal and at full term. The birth weight was 6 lb. 11 oz. (3,030 gm.). The infant had some difficulty in breathing, but this was relieved by placing her in a prone position. Tube feeding was employed for the first few days, after which she was given bottle feedings. At 6 days of age, the infant was discharged from the hospital. There was no family history of a cleft palate. The mother suffered no illness during her pregnancy.

Oral examination revealed an unusually small tongue closely attached to the floor of the mouth. In the course of our first examination under sedation, the infant became cyanotic and failed to initiate mandibular movements sufficient to permit the passage of air. This was relieved immediately by maintaining forward traction on the tongue and mandible. After about five minutes, the infant recovered control of mandibular movements, and respiration continued

normally. Aside from this isolated episode, which occurred under sedation, the parents did not report any similar difficulties. The child has continued to grow and develop at a satisfactory rate.

Growth Studies.—The casts disclose symmetrical cleft of the hard and soft palate, extending distally from the region of the nasopalatine foramen. Additional casts obtained at regular intervals revealed that the cleft had narrowed, so that it now presents a narrow V-shaped defect (Fig. 8).

The earliest lateral head plate, at 2 months 10 days of age, displayed a small mandible and a small tongue. The latter was positioned high and above the floor of the nose, but relatively remote from the posterior wall of the pharynx. The airway appeared sufficient to sustain respiration without any undue effort on the part of the infant. Progressive growth changes

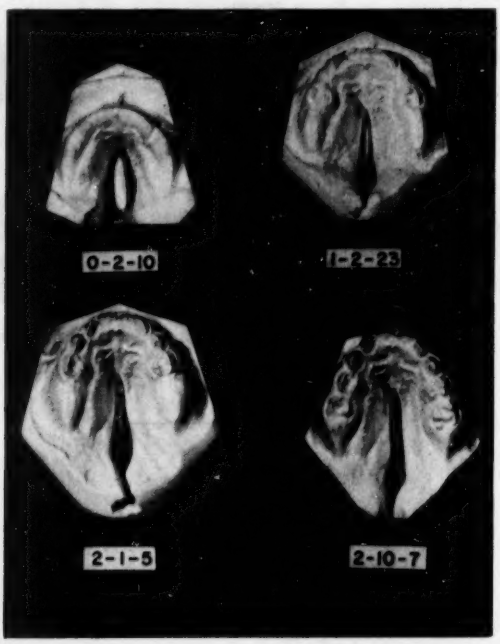

Fig. 8 (Case 2).—A series of casts of the maxillary arch from 2 months 10 days of age to 2 years 10 months 7 days. Note the progressive narrowing in the lateral dimensions of the cleft.

recorded up to the age of 3 years 4 months 13 days disclosed generalized growth in all areas of the face and cranial vault. Mandibular growth was continuous and progressively downward and forward (Fig. 9). During the period studied, from 2 to 40 months of age, the facial angle increased from 61.5 degrees to 68.5 degrees. The angle of convexity increased from 147 to 155 degrees. Altogether, the changes were in a direction tending to minimize the recessiveness of the chin in relation to the rest of the face.

Comment.—Micrognathia of itself is not sufficient to produce glossoptosis and respiratory embarrassment. If the tongue is large or even normal in size, the small recessive mandible will tend to displace the tongue distally and superiorly. It is this displacement that produces the respiratory obstruction both into the hypopharynx and into the posterior choanae. On the other hand, if the tongue is small, there will

be no obstruction of the airway, even in the presence of a micrognathic mandible. In this instance, the simultaneous occurrence of micrognathia and microglossia averted the respiratory difficulties commonly experienced in such instances.

The tendency to lose reflex control of the muscles of respiration and deglutition under anesthesia or sedation renders such procedures unusually hazardous in these patients because of the limited reserve. It is, therefore, important that such pro-

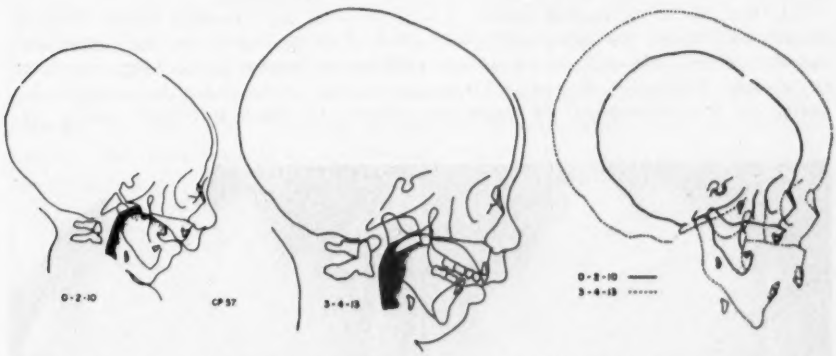

Fig. 9 (Case 2).—Individual tracings of the first film at 2 months 10 days of age, and the most recent film, at 3 years 4 months 13 days. The superimposed tracings on the right reveal the increment of growth during this period.

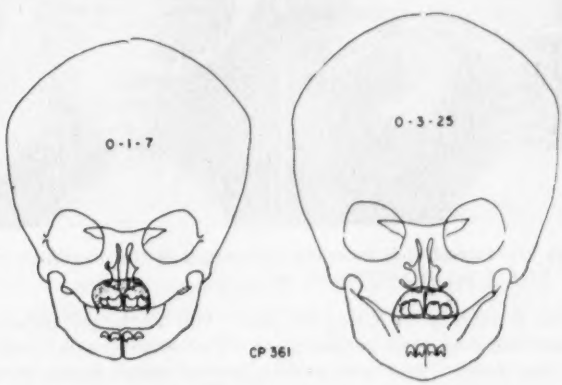

Fig. 10 (Case 3).—Tracings of posteroanterior head plates disclose the position in relation to the floor of the nose. At 1 month 7 days, the dorsum of the tongue occupied a considerable portion of the floor of the nasal chamber. At 3 months 25 days, the tongue had dropped down and no longer intruded into the nasal chamber to the same extent.

cedures be undertaken with full knowledge and anticipation of possible respiratory obstruction, in order that adequate emergency provisions for the establishment of an airway be available.

Case 3.—E. C., a white boy, aged 5 weeks, was referred to the outpatient clinic of the Cleft Palate Center for longitudinal growth studies. The delivery had been normal and at full term. His birth weight was 7 lb. 8 oz. (3,400 gm.). There was no history of a cleft on either

side of the family. No difficulty in breathing was encountered, and the infant was discharged from the hospital on the sixth day. After a brief adjustment period, the infant was readily fed by a combination of a hard nipple and by means of a premature baby bottle nipple.

Some snoring sounds were heard, especially as the infant was placed on its back and the head elevated with slight ventroflexion on the chest. The infant preferred to sleep on either side, and in these positions the snoring sounds were at a minimum. This baby showed progressive improvement, and at the age of 5 months he weighed 15 lb. 8 oz. (7,030 gm.).

Growth Studies.—Two sets of records are available in this case. The first was obtained at the age of 1 month 7 days and the second at 3 months 25 days of age.

The first cast of the maxilla revealed a wide parabolic cleft extending distally from the nasopalatine foramen. The widest portion of the cleft, at the level of the maxillary tuberosities, measured 16 mm. Although the second cast exhibited an increase in the length and width of the palate, there was a decrease of 1.5 mm. in the width of the cleft at its widest portion. During the first examination, the tongue was observed to occupy at rest the opening into

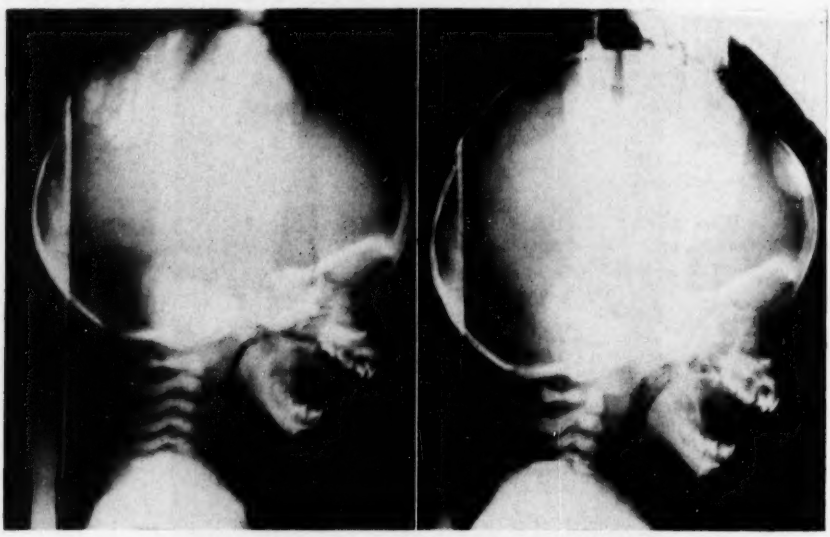

Fig. 11 (Case 3).—Lateral films revealing the changes in the dimensions of the pharynx from 1 month 7 days of age to 3 months 25 days.

the nasal chambers provided by the cleft in the palate. This was further confirmed by examining the frontal and lateral views of the head plates. The second series of films indicated that the tongue was now postured in a more inferior position and no longer occupied the nasal cavity to the same extent previously noted (Fig. 10). This new position of the tongue could be explained by the downward and forward growth of the mandible that had occurred in the interim.

In the first lateral film, the recessive chin, the distally and superiorly malposed tongue, and the relatively restricted airway were clearly observed. Two and one-half months later, considerable growth in the mandible had occurred to improve the facial profile, alter the posture of the tongue, and increase the anteroposterior diameter of the airway. The tongue was no longer in close apposition to the posterior pharyngeal wall, and its superior margin did not extend into the nasal cavity to the degree previously observed. Coincidentally, the mother reported a diminution of the stertorous breathing that had been present (Figs. 11 and 12).

Superimposition of the tracings of the bony structures revealed the rapid growth characteristic of this early period in life. In two and one-half months, the cranial vault and all parts of the face exhibited proportionate increases. Particularly encouraging was the amount and

direction of growth displayed by the lower jaw. Mandibular growth was responsible not only for reducing the glossoptosis and increasing the airway, but for the improvement in the appearance of this baby's face.

Comment.—The problem presented by this baby was unique and different from the two previous cases because of the partial obstruction of the airway. Diligent nursing care to determine the most comfortable position for breathing and feeding may be sufficient to tide such cases through their critical period. In some instances, the prone positioning and orthostatic feeding suggested in the literature are most successful. Again, one is impressed by the remarkable potential for prolific growth during this period of life; a potential that is shared by the small mandible. It follows then, that every effort must be made to permit the realization of the baby's potential for growth by providing an adequate airway, which, in turn, facilitates feeding. The clinical course to be followed is varied and depends on the severity of the symptoms and principally upon the degree of obstruction of the airway.

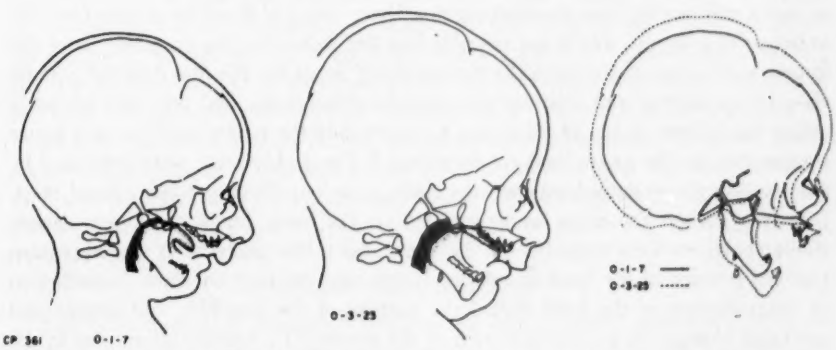

Fig. 12 (Case 3).—Individual tracings of the films in Figure 11 and the superimposed tracings to reveal the increment in growth.

COMMENT

The representative sampling of cases presented provides an answer to the questions which the study was designed to solve. It is observed from the data presented that the mandible possesses remarkable potentialities for growth in patients with the Pierre Robin syndrome. Thus, all efforts should be directed toward sustaining life in a metabolically favorable climate in order that a more physiologic airway may be established as growth proceeds. With growth, the glossoptosis is minimized and spontaneous resolution of the respiratory and feeding problems occurs. It is our opinion that tracheotomy should be resorted to promptly if respiratory embarrassment is significant, in order to achieve a sufficient airway to provide adequate oxygenation. This is undoubtedly a life-saving procedure in some patients.

On the basis of our longitudinal growth studies, certain prognostications concerning the future growth of the micrognathic mandible are permissible. In most instances, the increment in mandibular growth, as related to total facial growth, is sufficient to overcome the extreme recessiveness of the chin that is observed at birth. Since mandibular growth continues until late adolescence, it is possible to

hope for an esthetically pleasing profile in adulthood. The management of the cleft palate has been in keeping with the established criteria for the treatment of palatal defects.

The lateral cephalometric film served as a valuable diagnostic tool in estimating the degree of obstruction of the airway as a result of the glossoptosis. In our experience, there was a high positive correlation between the degree of obstruction revealed in the x-ray film and the incidence and severity of the respiratory difficulties. When obstruction of the air passage was complete and the tongue was practically in contact with the posterior wall of the pharynx, tracheotomy was recommended as a life-saving procedure. If the obstruction was incomplete, more conservative measures were employed. Care was taken to ascertain the most comfortable postures for breathing and feeding for the individual case, and the nurse or parent was carefully instructed in the care of the infant. Appropriate nipples were selected to minimize the energy expended by the infant in the feeding process.

In the course of these studies, we were aware of an obvious objection to placing so much reliance on these roentgenograms. Since many of these films were obtained under mild sedation, was it not possible that the posture of the mandible or of the tongue might have been altered by the sedative? Secondly, the film depicted a static view of the airway and represented only two dimensions. Did this view properly reflect the kinetic ability of the infant to manipulate the tongue and jaw and hence compensate for the restrictions on the airway? These objections were overruled by the consistent correlation between the findings in our films and the clinical state. Moreover, when the films were repeated in the same infant without sedation, similar postures were recorded for the structures under analysis. It was important that the posture of the head in relation to the neck be kept constant. Dorsiflexion or ventroflexion of the head varied the posture of the mandible and tongue and produced changes in the configuration of the airway. To indicate alterations in the posture of the head to the neck, our tracings purposely included at least the first two cervical vertebrae.

We recognize that few institutions possess cephalometric roentgenographic equipment. Therefore, we should like to point out that an ordinary lateral film obtained by carefully positioning the infant can provide useful diagnostic data. To minimize enlargement, a target-object distance of at least 3 ft. (90 cm.) is recommended. For the sake of definition and to further decrease enlargement, the object-film distance should be kept at a minimum. Sjölin [17] has published interesting films to describe his experiences with a case of micrognathia. Although his films did not permit quantification of the growth changes, they were adequate for diagnostic purposes.

A number of papers in the literature claim to "stimulate" the growth of the mandible by a variety of mechanical devices or surgical procedures. For example, a special nursing bottle was designed to force the infant to protrude his jaw in order to obtain nourishment and, by this protrusion, to stimulate mandibular growth.[4] From our data, we would conclude that the nursing care enabled the infant to survive until mandibular growth was sufficient to provide a more adequate airway.

In another report, continuous traction on the mandible was maintained by circumferential wiring around the symphysis. The authors claimed growth-stimulating

properties for this procedure.[9] From the findings in our series, it would seem that mandibular growth probably occurred spontaneously and not because of the stimulus provided by surgical traction.

The important and prime objective in the care of these children is to provide an airway. If possible, this should be accomplished with a minimum of trauma. Secondly, the infant's total needs should be assessed to provide optimal conditions for somatic growth. As the potential for growth is permitted to express itself, the chin grows downward and forward away from the base of the skull. With this pattern of growth, adequate space for the tongue is provided, the airway enlarges, and there follows a spontaneous resolution of the symptoms. Also, there is progressive improvement in the facial appearance.

There is another dimension to the abnormal posture of the tongue, as observed in these patients, that merits discussion. Not only does the tongue block the pharyngeal spaces, but it also occupies a segment of the nasal cavity. This finding revives the theory that during embryonic development the tongue failed to sink below the palatal processes and hence prevented their fusion. The high incidence of micrognathia in the population of clefts involving only the hard and soft palate lends support to this theory. Mandibular micrognathia is a physiological finding in early intrauterine life. If for some reason the micrognathia persists and fails to carry the tongue down and out of the nasal cavity, a cleft in the palate might result.

In early postnatal life, the tongue acts to keep the cleft palatal processes apart. As the tongue descends with mandibular growth and no longer forcefully intrudes itself into the nasal cavity, the palatal processes tend to approximate in the midline. Fusion of the palatal processes cannot occur, but the narrowing in the cleft is a recorded fact.

SUMMARY AND CONCLUSIONS

The development of accurate techniques for cephalometric roentgenography of infants has made possible a longitudinal study of the growth of the micrognathic mandible. As a result of these studies, useful diagnostic and prognostic information has been obtained to provide a rationale for the management of individual cases.

The lateral cephalometric roentgenogram is a valuable diagnostic aid in assessing the severity of the glossoptosis and its obstruction of the airway. A definite correlation exists between the degree of constriction of the airway and the severity of the clinical state. On the basis of these findings, it is possible to recommend either conservative management or tracheotomy in extreme situations. Three cases, out of a larger series of similar cases, were presented to indicate the spectrum of variations to be encountered.

In all instances, it was found that where an adequate metabolic situation was provided and the infant gained in weight, mandibular growth during the first few months was sufficient to provide for a natural resolution of the symptoms attending the glossoptosis.

Longitudinal records have indicated that mandibular growth is proportionally adequate to reduce the retrognathic profile and provide an esthetically harmonious facial appearance.

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LEUKEMIC XANTHOMATOSIS

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WE SHOULD like to present a heretofore unknown disease, "leukemic xanthomatosis." The condition is not familial or hereditary and is characterized by the following features:

1. Xanthomatous skin lesions of the disseminated type and normal cholesterol blood levels.
2. Development of generalized visceral reticuloendotheliosis with increased cholesterol tissue contents, a dense argyrophilic reticulum, and the appearance of foam cells—a histological picture similar to that of Hand-Schüller-Christian disease and its variants.
3. Deposits of foci of primitive mesenchymal cells in the affected tissues—as commonly seen in leukemia—however, with many of these cells exhibiting a foamy protoplasm due to a high cholesterol content.
4. Leukemic blood—and bone marrow findings and a fatal course as in leukemia.
5. Numerous inclusion bodies were found in the organs of the presented case, and a virus was considered as a possible etiological agent.

In the aleukemic forms, the primitive stem cells do not differentiate into blood cells, but only into histiocytes and fibroblasts. This development has been described* in the following conditions:

1. Juvenile xanthoma, the childhood form of normocholesteremic[1] xanthoma of the disseminated type.†
2. Letterer-Siwe disease.[5]
3. Hand-Schüller-Christian disease.
4. Generalized lipogranulomatosis.
5. Eosinophilic granuloma of the skeleton.

A similar course is the rule in Hodgkin's disease. However, in this condition more and more cases are being reported where the proliferating cells developed not only into histiocytes and fibroblasts, but also into hematic elements.‡

From the Department of Pediatrics (Dr. Freud and Dr. Luhby) and the Departments of Pathology and Clinical Pathology (Dr. Plachta and Dr. Speer), New York Medical College, Flower and Fifth Avenue Hospitals.

* References 6 and 7.

† References 2-4.

‡ References 8-28.

In the leukemic variant of xanthomatosis (xanthomatous reticulosis), the stem cells are differentiating into two directions—into histiocytes and fibroblasts, on the one hand, and into hematic cells, on the other—thereby producing leukemic phenomena. This event imprints its gravity on the course of the condition.

But for the finding of innumerable foci of extramedullary hematopoiesis, the histological picture is identical with that of the aleukemic forms, permitting its classification as a variant of the basic process—xanthomatous reticuloendotheliosis.

Downey [29] used the term leukemic reticuloendotheliosis when referring to leukemia with a primary irreversible hyperplasia of the reticuloendothelium. He believed that the majority of these cases show an involvement of the reticulum in which the free cells are differentiating toward some type of blood cell other than the monocyte and regarded many of the cases of monocytic leukemia as a variety of myelogenous leukemia.

Klemperer [30] stated that hematopoietic activity of the adult reticulum is not observed under normal conditions, probably because an abundant store of hematic cells is readily available. But under the influence of excessive demands, as in severe anemias or blood dyscrasias, the supply of hematic cells in the normal sites of blood formation becomes exhausted, and heteroplastic formation of these cells from the reticulum reveals itself. In cases of Gaucher's disease, hematopoiesis is normal, but in their spleens extramedullary blood formation can be conveniently observed because of the conspicuous reticulum. A study of these pathological conditions indicates that the adult cytoplasmic reticulum retains the embryonal potentialities and may, under the influence of adequate stimuli, develop into any of the four directions: histiocytic (phagocytic), fibroblastic, hematic, or endothial cells.

Israels [31] described six cases of "aleukemic myeloid reticulosis," ranging in age from 3½ to 56 years. They all presented splenomegaly, infiltration of the bone marrow with "abnormal reticulum cells," severe anemia, and a rapid fatal course. A similar case was seen by Keech and Scott.[32] A case of acute systemic reticuloendotheliosis terminating in monocytic leukemia was described by Gray and Taylor.[33] Orchard [34] reported a case of Letterer-Siwe disease in a 3½-year-old patient where the stem cells showed unmistakable differentiation into histiocytes, as well as into hematic cells, with the appearance of hemohistiocytes in the peripheral blood stream. Keizer [35] saw two young children with malignant reticuloendotheliosis and found at autopsy the differentiation of primitive stem cells into histiocytes and lymphatic elements.

This development is hardly known in xanthomatosis. In a personal communication, Thannhauser [36] wrote, "I have wondered very often why we did not see at least sometimes an increased white cell count in eosinophilic xanthomatous granuloma similar to that we see once in a while in Hodgkin's disease." There are only two reports of cases of normocholesteremic xanthomatosis in the literature where significant changes in the blood picture were observed. Laymon and Sevenants [37] saw a case of generalized lipoid granulomatosis in a young child which showed an increase in the myeloid elements in the sternal bone marrow, and Thelander and co-workers § described a case of generalized xanthomatosis with involvement of skin and visceral organs and a blood picture (high white cell counts with many immature myeloid elements) that they called "not unlike myelogenous leukemia."

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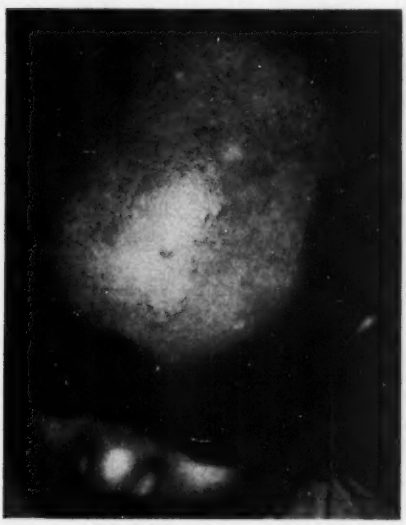
REPORT OF CASE

In 1951, one of us (P. F.) [6] described in the framework of a general discussion of systemic reticuloendotheliosis the course of a case of xanthoma disseminatum (Fig. 1) with a chronic myeloid response. In the following, an abstract of this report which covered the period from 1948 to January, 1951, is given, a few facts from the case history which we discovered only now are added, and the progress of the condition from January, 1951, until June 14, 1951, when the child died, is described.

J. M., a boy of Puerto Rican extraction, was born on April 4, 1946, in the Metropolitan Hospital. The family history was noncontributory. The findings at birth were entirely normal. The skin was clear. Xanthomatous lesions were first noticed when he was readmitted to this hospital on March 14, 1948. The mother, at that time, said that she had regarded his skin condition as birth marks and did not know how long the child had had them. In September, 1948, the child was admitted to another hospital, where the diagnosis of xanthoma disseminatum was confirmed. At this time, the serum cholesterol was 303 mg. per 100 cc., with 199 mg. per



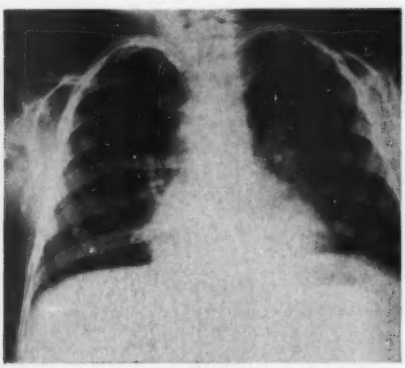


Fig. 1.—Xanthomatosis of the scalp; hemorrhagic lesion on the forehead (reproduced with permission from *The Journal of Pediatrics*).

Fig. 2.—Miliary infiltration of both lung fields (reproduced with permission from *The Journal of Pediatrics*).

100 cc. esters. He had an acute upper respiratory infection. His white blood cell count was 13,700, with 71% polymorphonuclear cells, of which 14% were staff cells and 25%, eosinophiles.

He was admitted to the Flower and Fifth Avenue Hospitals on Feb. 4, 1949, and the diagnosis of xanthoma disseminatum was proved by biopsy. The total serum cholesterol was 199 mg. per 100 cc., with 112.2 mg. per 100 cc. esters, and remained normal until the child died. The bone marrow was hyperactive, but a definite diagnosis of a leukemic response could not yet be made (Dr. Speer).

The child ran a course characterized by remissions and relapses during the period from February, 1949, until January, 1951. An x-ray picture of the chest taken in November, 1949, revealed thickening of the hilar shadows and fine miliary infiltration extending into both lung fields (Fig. 2), compatible with xanthomatous involvement.

In April, 1949, the child was able to go home, being in a state of complete clinical remission, and was readmitted in November, 1949, for another month. The child had now developed pronounced hepatosplenomegaly and had lost considerable weight. Toward the end of December, 1949, there was another remission, which made it possible to send the child home. He had to be readmitted with a severe respiratory infection on March 29, 1950. Peripheral and bone marrow findings at that time were similar to those of chronic myeloid leukemia. The total serum choles-

terol was 101 mg. per 100 cc., with 36.2 mg. per 100 cc. esters. During these hospital stays, biopsies of lymph nodes had been done, and, as anticipated, reticuloendotheliosis was found, eventually, more than two years after skin lesions had been noticed, April 26, 1950 (Fig. 3). X-ray treatment and blood transfusions seemed to have a favorable influence on the condition. In October, 1950, both peripheral counts and bone marrow examinations revealed the presence of a hemopoietic pattern similar to chronic myeloid leukemia. Toward the end of this month, the patient was discharged strikingly improved and was seen regularly in the clinic for blood cell counts and bone marrow examinations.

He was readmitted with the chief complaint of severe nosebleeds, on Jan. 17, 1951. The xanthomatous lesions had decreased in number. They were found behind the left ear, in the scapular region, and on the scalp. Physical examination revealed a chronically ill, very cachectic, and pale child. There were numerous small and large ecchymotic areas scattered over both lower extremities and generalized lymphadenopathy: large freely movable lymph nodes were present in both anterior cervical chains, in the axillae, and in the inguinal regions. An x-ray picture of the chest taken on Jan. 18, 1951, showed the hilar shadows to be markedly thickened, with a suggestion of lymphadenopathy on the left side and diffuse miliary infiltration extruding

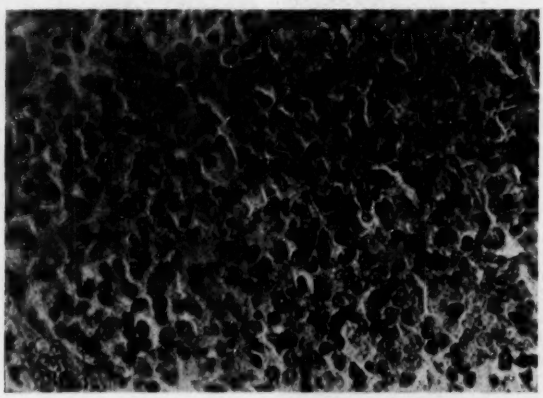


Fig. 3.—Lymph node biopsy: tissue architecture replaced by profuse reticuloendotheliosis (reproduced with permission from *The Journal of Pediatrics*).

into both lung fields. The liver edge was palpable 5 fingerbreadths below the costal margin, sharp, but not nodular. The spleen could be felt 6 fingerbreadths below the costal arch, near the pelvic brim. The spleen was firm. There was pronounced protrusion of the abdomen (Fig. 4). These findings were confirmed by an x-ray of the abdomen taken on Feb. 12, 1951, showing marked diffuse enlargement of the abdomen. The splenic and liver shadows were markedly enlarged. There was diffuse haziness of the abdomen, probably due to ascites. Total cholesterol was 114.4 mg. per 100 cc., esters, 35.1 mg. per 100 cc. A second series of x-ray radiations was started on Jan. 19, 1951, to the spleen, with 108 r per field. The patient was quite debilitated but alert and moderately active. His appetite was erratic. His greatest distress was caused by frequent paroxysms of cough, which was dry, hacking, and nonproductive and became markedly worse at night. Medication failed to ameliorate the cough.

On Feb. 2, 1951, severe epistaxis developed. Anterior nasal packing was necessary. The cough continued. The patient became quite irritable, and his appetite diminished. The temperatures were frequently elevated. Epistaxis recurred every two to three days. On Feb. 18, 1951, petechiae were noted on both the buccal mucosae and on the palate. There were fresh ecchymotic areas on the extremities. Repeated blood transfusions were given during this period. For an interval of four days the child improved symptomatically. The temperature was normal. There

were no nosebleeds, and the cough seemed less distressing. The breath sounds appeared essentially normal to auscultation. Liver and spleen were thought to be slightly smaller, though the size of the abdomen appeared unchanged.

On Feb. 22, there was a sudden temperature spike to 103 F. Coughing became more severe, and the child was listless. He refused medications and food, and on the same evening another severe nasal hemorrhage occurred. The temperature remained elevated, and the child was quite lethargic. There was a loss of 7 lb. (3.2 kg.) since his admission, when the weight was 36 lb. (16.3 kg.). The diagnosis of radiation sickness was considered at that time.

On Feb. 23, another blood transfusion was given, and chloramphenicol (Chloromycetin) was administered by rectum (250 mg. every four hours) from this day until March 5. During this time, the child became more active, and his appetite increased, but he appeared very pale and emaciated, and his abdomen was excessively protuberant. On March 17, 200 cc. of fresh blood was transfused, and urethan therapy was started on March 15. The child had had no nosebleeds

Fig. 4.—Cachexia and pronounced protrusion of the abdomen. Hepatosplenomegaly.

for about 10 days, when another severe hemorrhage occurred. Thereafter, these episodes became very frequent. Another transfusion was given on March 31. Between April and June, the cough paroxysms became more severe and more frequent, occurring during day and night. There were episodes associated with shortness of breath and severe dyspnea. At times, coughing initiated aggravated epistaxis. The child demanded copious amounts of water in an effort to alleviate the irritation of his throat. Fluid intake ranged at this time between 1,200 and 2,200 cc. per day.

In April, numerous petechiae were noted on the patient's face and shoulders. The temperature spiked to 102 F. The child was very pale and irritable. A chest x-ray taken on April 9 showed further extension of the peribronchial infiltration radiating into both lung fields and bases. On April 12, the peripheral white cell count had risen to its highest peak of 231,000. Physical examination of the chest revealed coarse breath sounds of both midlung fields and bases. Blood transfusions were given on April 12 and April 28. Urethan therapy was continued, and triethylenemelamine (2.5 mg.) was taken orally on April 19, 23, and 30, on May 10 and 23, and on June 9.

Repeated measurements of the spleen and liver were as follows:

	Inches Below Costal Margin	
	Spleen	Liver
4/17/51	4.75	4.25
4/27/51	5.0	4.25
5/ 3/51	5.5	4.2
5/ 9/51	5.5	4.0
5/22/51	5.5	3.5
6/ 3/51	4.75	3.75

Clinically, the patient improved after the administration of triethylenemelamine. during April and May. Although still coughing, he became more cheerful and active, and his appetite increased. The temperature became normal, and we were considering sending the child home for a while.

During the first week of June, however, temperature elevations recurred, rising during the second week to 103.5 F. The temperature pattern could not be influenced by antibiotics and chemotherapy. Urethan treatment was omitted for a day and the dosage decreased thereafter. An x-ray of the sinuses taken on June 6, 1951, showed clouding of the right maxillary antrum and left ethmoid cells. A chest x-ray taken on the same date revealed fine nodular infiltration extending into both lung fields, especially marked in the bases. There were never any significant urine findings, and the tests for Bence Jones protein body were always negative.

The child became much weaker. On June 12, his state changed continually from lethargy to hyperirritability. His color was waxen. Frequent paroxysms of severe cough recurred, and there were frequent episodes of vomiting. Practically all fluids and foods were refused. On June 14, profuse epistaxis developed, and a blood transfusion was ordered on that day. However, at 4 p. m., the child became markedly lethargic and was aroused with difficulty. Forced grunting expirations were heard. At about 4:30 p. m., the child had a convulsive seizure and lapsed into a semicomatose state. Physical examination revealed generalized studding of the entire body and extremities with fine petechiae. Thereafter several convulsive seizures occurred, and fine tremors of the hands were noted. The pulse became rapid and very feeble, and at 9:03 p. m. the child died.

It should be mentioned here that repeated unsuccessful attempts were made to influence the course of the condition with high doses of antibiotics (up to 1,600,000 units of penicillin, 1,500 mg. of oxytetracycline [Terramycin], 1,500 mg. of chloramphenicol per 24 hours, and triple sulfonamides [1 grain per pound (0.07 gm. per 0.5 kg.) of body weight in 24 hours] given separately and combined for extended periods of time).

The blood findings from Jan. 16 until June 14, 1951, can best be seen in Table 1.

Autopsy.—Gross Findings: The body weighed 28 lb. (12.7 kg.) and measured 37.5 in. (95.3 cm.). The head was well shaped. The scalp was covered by sparse dark hair, and there were scattered pale yellow-gray, oval, rounded, or irregular xanthomata. These were sessile or slightly raised and measured up to 0.8 cm. in diameter. They were also noted over the neck and left shoulder. The abdomen was scaphoid. The liver extended 5.5 cm. below the costal margin in the midclavicular line and 1.5 cm. below the xiphoid. The spleen extended 6.5 cm. below the costal margin.

The thymus and thyroid glands were of normal consistency and appearance.

The heart weighed 150 gm., was globular, and measured 5.2 cm. across the base and 5.4 cm. from base to the rounded apex. There was a hydropericardium (350 cc. of clear straw-colored fluid). The translucent epicardium revealed scattered petechiae. The tricuspid valve, chordae tendineae, and endocardium were of normal consistency and appearance. The right ventricular myocardium was hypertrophied. The pulmonary valve was normal. The foramen ovale and ductus arteriosus were obliterated. The mitral valve leaflets, chordae tendineae, and ventricular endocardium were opaque. The left atrium and ventricle were dilated, and the left myocardium was hypertrophied. The aortic valve leaflets, the arch of the aorta, and the coronary arteries were of normal architecture and consistency. The measurements of the tricuspid, pulmonary, aortic, and mitral valves were 3.6 cm., 2.2 cm., 2.5 cm., and 3.5 cm., respectively.

TABLE 1.—*Blood Findings from Jan. 16, 1951, to June 14, 1951*

Date	% HGB.	RBC	WBC	PMN. Mat.	PMN. Immat.	Eosinophiles	Basophiles	Lymphocytes	Monocytes	Neut. Myelocytes	Eos. Myelocytes	Promyelocytes	Metamyelocytes	Blast Cells	Erythroblasts/ 100 WBC	Platelets
1/16/51	57	4,100,000	111,000	88	2	3	..	7	..	34	..	2	8	..	Occas.	150,000
1/30/51	49	2,400,000	84,000	38	4	7	1	25	6	6	2	4	4	3	5	45,000
2/ 6/51	45	2,900,000	174,000	41	2	3	..	31	8	10	..	2	1	2	9	75,000
2/12/51	54	3,300,000	78,800	46	2	3	..	31	5	8	1	..	2	2	3	45,000
2/19/51	52	3,100,000	60,000	38	9	4	..	14	4	15	2	4	5	5	8	70,000
2/21/51	62	3,450,000	107,000	36	9	1	1	23	4	11	1	4	6	5	3	60,000
2/26/51	71	3,600,000	60,000	..	..	..	..	..	..	..	..	..	..	..	..	115,000
3/ 2/51	59	3,000,000	.....	..	..	..	..	..	..	..	..	..	..	..	..	70,000
3/17/51	38	2,220,000	93,800	35	9	5	..	19	4	10	2	5	5	6	30	.....
3/21/51	48	2,500,000	110,000	..	..	..	..	..	..	..	..	..	..	..	..	85,000
3/22/51	44	2,200,000	.....	..	..	..	..	..	..	..	..	..	..	..	..	150,000
3/27/51	42	2,750,000	.....	..	..	..	..	..	..	..	..	..	..	..	..	25,000
3/28/51	38	2,080,000	161,000	..	..	..	..	..	..	..	..	..	..	..	..	210,000
4/ 2/51	42	2,450,000	113,000	33	3	9	..	13	10	4	..	6	1	4	17	150,000
4/ 5/51	45	2,620,000	162,000	29	7	8	3	7	6	4	..	4	3	5	24	60,000
4/10/51	43	2,500,000	113,500	35	5	13	3	15	9	5	..	5	3	7	26	65,000
4/12/51	34	2,010,000	231,000	48	13	..	..	2	..	30	3	..	4	2	..	.....
4/19/51	42	2,250,000	130,000	29	10	6	..	6	6	20	5	3	9	6	..	.....
4/20/51	42	2,290,000	184,000	35	7	..	..	1	..	31	5	2	9	5	Numerous	205,000
4/24/51	44	2,340,000	80,380	46	8	9	1	..	6	16	2	4	5	3	27	80,000
4/27/51	36	2,200,000	103,700	40	4	..	..	9	10	25	6	..	..	7	Numerous	35,000
5/ 1/51	54	2,800,000	83,000	58	8	7	..	2	8	11	..	1	4	1	Numerous	50,000
5/ 5/51	54	2,600,000	38,000	56	10	3	..	4	5	12	1	2	5	2	Numerous	80,000
5/15/51	55	3,300,000	34,900	52	5	5	1	8	5	15	1	4	1	2	Numerous	110,000
5/22/51	55	2,860,000	32,800	26	9	8	2	14	6	16	2	7	7	3	51	110,000
5/25/51	54	3,820,000	21,400	..	..	..	..	..	..	..	..	..	..	..	..	130,000
5/29/51	52	3,020,000	25,500	40	11	5	..	15	4	13	1	3	6	2	..	160,000
6/ 5/51	60	3,000,000	35,000	37	8	2	1	21	6	13	..	4	5	3	51	75,000
6/ 9/51	61	3,150,000	40,000	27	11	1	5	8	10	10	..	..	10	6	89	55,000
6/12/51	56	2,600,000	15,700	33	4	2	..	24	7	10	..	3	12	4	42	65,000
6/14/51	49	2,900,000	39,000	28	5	7	3	19	7	13	..	1	15	2	271	.....

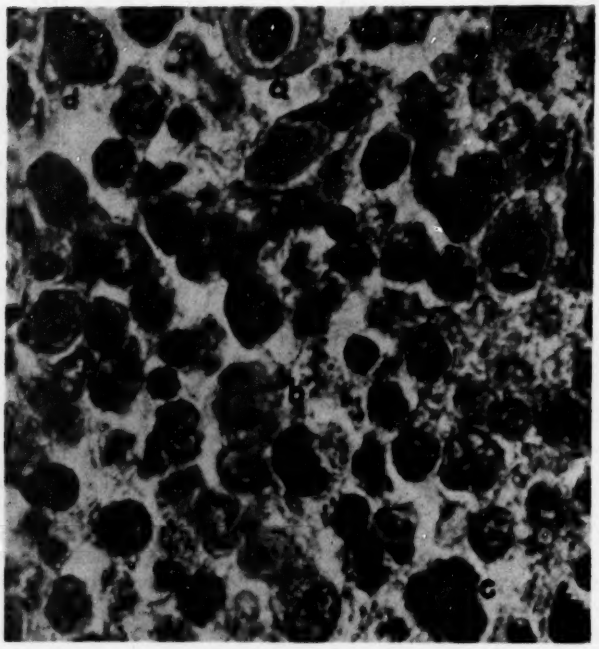


Fig. 5.—Spleen: active reticuloendothelial proliferation containing (*a*) multiple inclusion cells; (*b*) primitive foam cells; (*c*) and (*d*) undifferentiated cells (× 220).

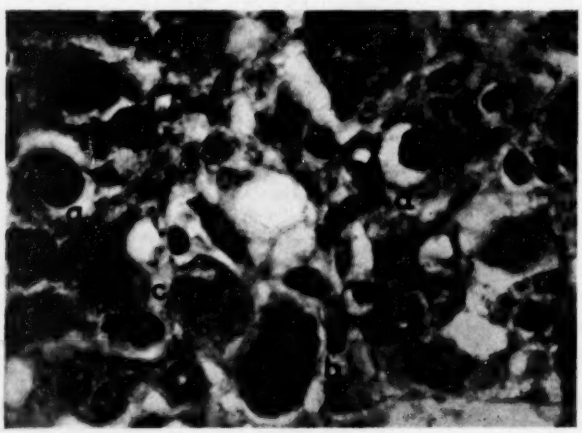


Fig. 6.—Liver: (*a*) inclusion cells; (*b*) undifferentiated cells; (*c*) primitive foam cells in an active reticuloendothelial architecture (× 420).

The combined weight of the lungs was 750 gm. The translucent pleura covered a purple-blue mottled-with-gray, firm, and rubbery parenchyma. The trachea and bronchi contained frothy hemorrhagic fluid. The mucosa was highly congested. There was edema, pneumonitis, atelectasis, and focal emphysema.

The spleen weighed 680 gm. and was of firm consistency. There was marked congestion. The fibrous markings and malpighian corpuscles were obscured. The pulp scraped with ease.

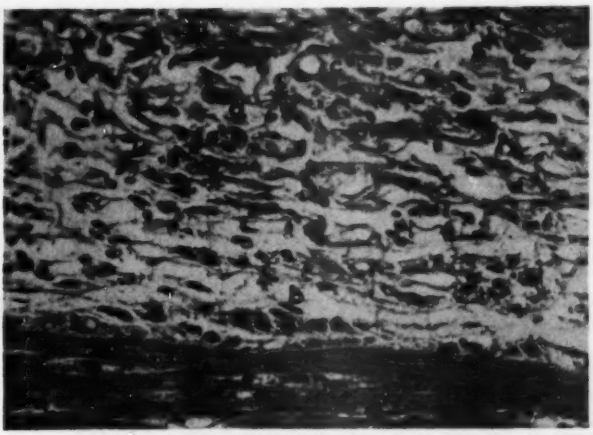


Fig. 7.—Heart: (*a*) undifferentiated cells; (*b*) primitive foam cells in an edematous subepicardium; (*c*) a row of inclusion cells (× 80).

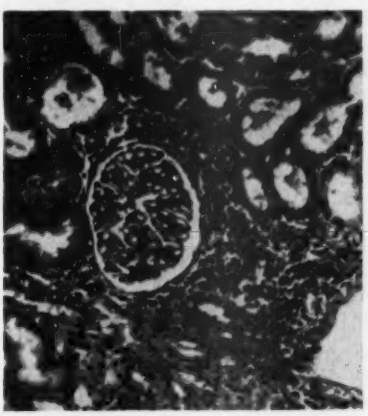


Fig. 8.—Kidney: histiocytic reticuloendothelial proliferation with active myeloid and monocytoid reaction; absence of karyokinesis (× 60).

The liver weighed 990 gm. There was perihepatitis at the midportion, running along the falciform ligament. The cut surface revealed a congested parenchyma.

The combined weight of the adrenal glands was 6.5 gm.

The kidneys each weighed 52 gm. The cortical surface was lobulated. On section, the cortical and medullary surfaces were well differentiated and of the usual consistency and architecture.

The bone marrow appeared highly hyperplastic.

The gastrointestinal tract revealed no significant findings.

The bladder, prostate, and testicles were of normal consistency.

The cervical, mediastinal, bronchial, peribronchial, and inguinal nodes revealed moderate to severe congestion and adenopathy.

The pituitary gland revealed no gross abnormality.

The frontal, occipital, and both temporal bones measured 0.3 cm., 0.2 cm., and 0.2 cm. in thickness, respectively. The dura was markedly congested. The brain weighed 360 gm. The

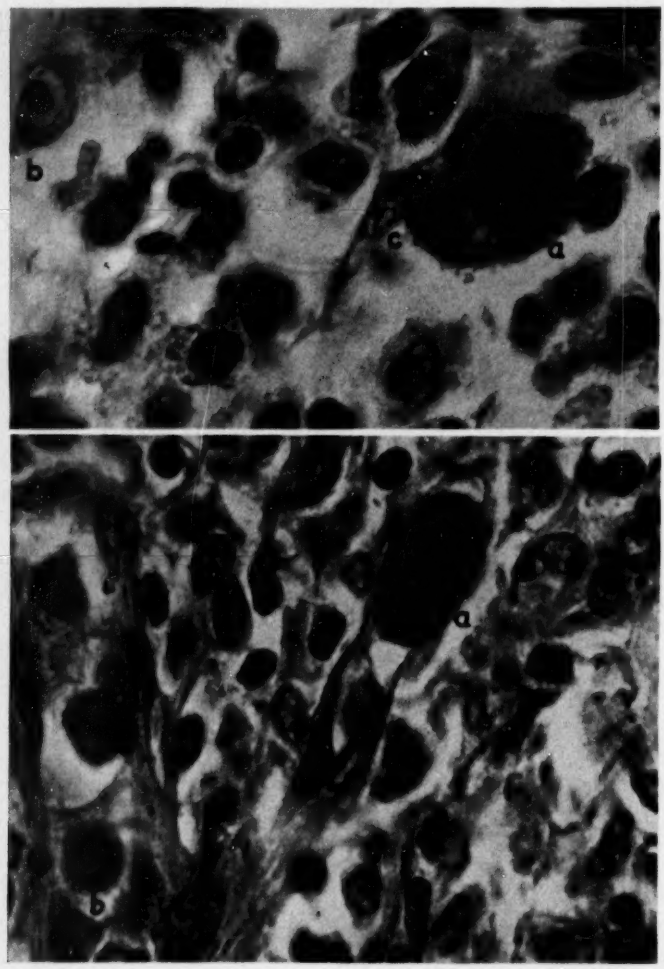


Fig. 9.—Lymph node: (*a*) undifferentiated multinucleated giant cells mirroring megakaryocytes showing cellular division without separation and atypical giant cells containing thick-rimmed, oval, and angular nucleus; (*b*) inclusion cells; (*c*) undifferentiated cells free from particulate matter, spindle-shaped, with fine branched processes (× 780).

convolutions revealed severe congestion, chiefly in the region of the midcerebral artery and vessels composing the circle of Willis and those of the basilar vertebral vascular channels. The cut surfaces of the cerebrum, cerebellum, pons, medulla, and cord showed severe congestion, petechiae, and peripheral edema.

Microscopic Findings: The morphological appearance of lymph nodes, bone marrow, spleen, liver, lungs, heart, kidneys, thymus and thyroid glands, testes, intestines, and other viscera showed a striking atypical cytogenesis, consisting of a variety of cellular components among which undifferentiated cells, many of them exhibiting a foamy protoplasm, found near or in the vicinity of small blood vessels, constituted a conspicuous finding. These cells were characterized by an oval, somewhat flattened, and pale nucleus found in a colorless nucleoplasm with scanty chromatin assuming the form of irregular strands. In some of these primitive mesenchymal foamy stem cells, a solitary nucleus was found to be oval or rounded and occasionally angular. Many of the cells were characterized by a distinct nuclear membrane. The latter nucleoplasm was traversed by a few fine chromatin threads, giving it a vesicular, faintly acidophilic, granular appearance. Additional components not observed in normal cytogenesis were characterized by a rounded nucleus surrounded by a sharply outlined narrow rim of opaque acidophilic cytoplasm. The nuclear membrane in the latter cells was thick, and the nucleoplasm was obscured by a closely set coarse chromatin. No nucleolus was apparent. Giant forms resembling megakaryocytes were also observed. A cell constantly found in close association with the undifferentiated cells was polygonal in character, with distinct outline, having a nongranular faintly basophilic cytoplasm. This noted histiocytic reticuloendothelial proliferation was found in association with active extramedullary hemopoiesis of the myeloid and monocytoid cell series. Commonly, eosino-

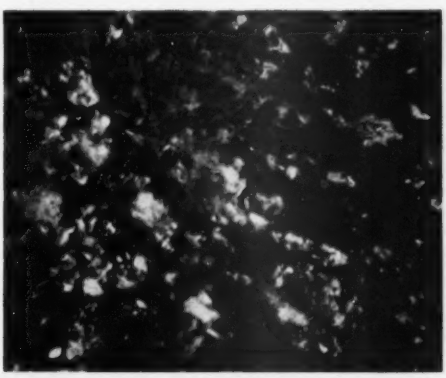


Fig. 10.—Lymph node: polaroid study showing diffuse lipoid content (× 90).

phile but also neutrophile and basophile myelocytes obliterated the normal architecture of the lymphoreticular stroma in which karyokinetic activity was seldom observed (Figs. 5 to 8).

The architecture of lymph nodes and parts of the spleen and other viscera was completely wiped out and their tissue replaced by a syncytium of primitive mesenchymal cells, many of them exhibiting a foamy protoplasm (Fig. 9). The cell components were enmeshed in a delicate reticular network. Preparations fixed by the Altmann-Gersch freezing method and studied with scarlet red, Best's carmine, and Sudan III demonstrated abundant cholesterol accumulation. Innumerable double refractile lipoid bodies could be observed with the polaroid microscope (Fig. 10), and chemical tissue analysis, as seen in Table 2, revealed high cholesterol figures.

It can be seen from this table that the cholesterol content of the skin lesions was more than 10 times that of normal skin, which corresponds to the figures determined in this type of pathology by Thannhauser.‖ The cholesterol content of the lymph nodes and spleen was about three times that of the normal organs. Other viscera showed a one and one-half-fold to two fold increase in cholesterol.

Cellular division without cellular separation produced a mirror image of multinucleated cells. A striking cellular component was an atypical giant cell with a distinct circular outline, possessing a granular faintly basophilic cytoplasm containing a thick-rimmed oval, angular, or round nucleus

‖ Reference 3, p. 359.

with a distinct halo. The nucleoplasm was basophilic and granular, the latter containing inclusion bodies, some of which were angular, others asteroid, in appearance. These inclusion-body cells were conspicuous in the adrenal glands and a common finding in either compact or sparse arrangement, distributed throughout the parenchyma in all affected viscera and in the lymphoreticular stroma.

There was a pronounced pericarditis characterized by reticuloendothelial hyperplasia extending into the edematous interstitia. Focal endocardial fibrosis and coronary artery medial hypertrophy were also found.

Pulmonary edema, hemorrhage, atelectasis, and focal emphysema were observed in the lungs. Inclusion cells were noted in the alveolar septa, in the alveolar spaces, and in the pulmonary vascular channels (Fig. 11).

The splenic cellular components were enmeshed in a network of a delicate reticulum (studied by the method of Foot, Krajian, Bielschowsky, and Laidlow's silver impregnation). Perisplenitis, hemosiderosis, and infarction were added findings.

Hepatic peripheral and central active reticuloendothelial proliferation and extramedullary hemopoiesis in the periportal spaces were conspicuous. Here, as noted above, inclusion cells were commonly encountered.

The adrenal gland architecture was obscured by the atypical cytogenesis in which inclusion bodies were a dominant finding (Fig. 12).

Subacute and chronic glomerulonephritis, interstitial edema, and focal hemorrhage were observed in the kidneys. Inclusion cells were not uncommon.

TABLE 2.—*Cholesterol Content of Tissues**

(Values Expressed as Percentages of the Dry Weight of Tissues)

	Skin Lesion	Normal Values, Skin	Lymph Node	Spleen	Normal Values, Lymph Node & Spleen	Liver	Normal Values, Liver	Kidney	Normal Values, Kidney	Lung	Normal Values, Lung
Total	4.11	0.15-0.3	5.89	4.95	0.6-2.3	3.84	2.1-2.6	2.57	1.5-2.8	5.05	1.2-2.7
Free	0.76	.....	3.72	3.2	0.5-1.1	2.5	0.44-0.55	2.2	0.9-1.1	3.89	0.7-1.0
Esters	3.35	.....	2.17	1.75	0.2-1.2	1.34	1.5-2.15	0.37	1.5-1.7	1.16	0.4-1.7

* Normal values from S. J. Thannhauser.[8]

The bone marrow was characterized by the atypical cytogenesis described above. Here too, many inclusion bodies were seen.

Multiple dermal xanthomata containing multinucleated giant cells and showing foamy reticulohistiocytic activity were a noted finding (Fig. 13), and double refractile lipoid bodies were well demonstrated by Polaroid study.

The cerebral and cerebellar cortex and medulla showed moderate edema, severe congestion, and perivascular areas suggestive of reticuloendothelial hyperplasia.

The anterior and posterior lobes of the pituitary were highly congested.

Final Diagnoses: The final diagnoses were leukemic reticuloendotheliosis (leukemic xanthomatosis) in lymph nodes, bone marrow, spleen, liver, lungs, heart, adrenals, kidneys, thymus, thyroid gland, gastrointestinal tract, brain, and pituitary gland; multiple xanthomata of scalp, neck, and back; pericarditis—adhesive, focal, acute, and chronic; hypertrophy of the myocardium; dilatation of the left ventricle and the right auricle; edema, pulmonary; pneumonitis—bilateral, focal, and diffuse; atelectasis and focal emphysema; splenomegaly—leukemoid, congestive; perisplenitis—acute and chronic; hemosiderosis; hepatomegaly; hepatitis—acute and chronic, leukemoid; adrenalitis—acute and chronic; glomerulonephritis—subacute and chronic; cerebral edema; congestion of viscera.

COMMENT

The development of systemic reticuloendotheliosis was anticipated at a time when the lesions were still restricted to the skin. Only 25 months after skin lesions had first been seen, reticuloendotheliosis was found in a lymph node. On the other hand,

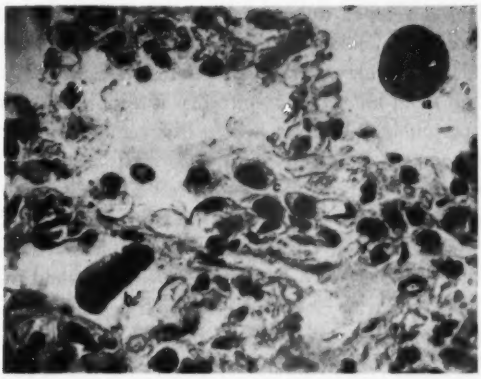


Fig. 11.—Lung: (*a*) inclusion cells; (*b*) undifferentiated reticuloendothelial cells in a reticuloendothelial activity showing (*c*) many primitive foam cells (× 110).

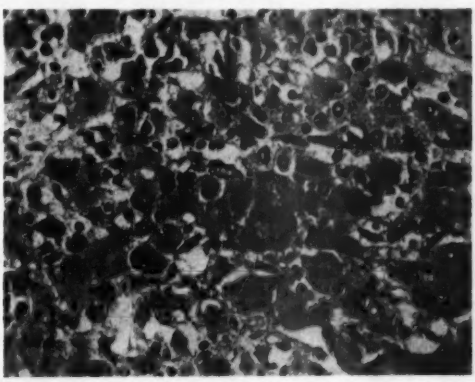


Fig. 12.—Adrenal gland, high power: (*a*) conspicuous inclusion cells in an architecture of active histiocytic proliferation (× 110).

Fig. 13.—Skin: reticuloendothelial proliferation showing (*a*) inclusion cells beneath the corium bordering the basal layer; (*b*) multiple giant cells; (*c*) foam cell histiocytes (× 40).

leukemic phenomena developed rather early, and one year after xanthomatous skin lesions had been noticed, a leukemic response was already suspected. The onset of an abnormal blood picture may, perhaps, be dated to Oct. 2, 1948, when, with the patient convalescing from an upper respiratory infection, his peripheral blood cell count was 13,700 per cubic millimeter, with a differential count showing 71% polymorphonuclear leucocytes, of which 41% were staff cells and 25% eosinophiles. While not conclusive, the extreme shift to the left in the differential count without the presence of a severe infection and with the high amount of eosinophiles might have been suggestive of the onset of a leukemic response. In February, 1949, the peripheral blood cell count revealed occasional myeloblasts and promyelocytes and a given percentage of myelocytes, metamyelocytes, and band forms. Still, there was no significant anemia present, and the blood platelets were normal; at this time the

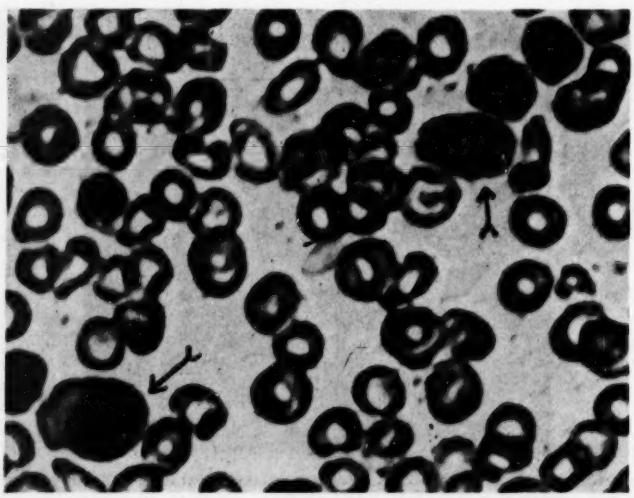


Fig. 14.—Large immature monocytoid cells with indented and elongated nucleus indicated by arrows (reproduced with permission from *The Journal of Pediatrics*).

bone marrow did not show an activity permitting the clear-cut diagnosis of a leukemic reaction.

During the next 13 months, while the patient was clinically well but for occasional rather severe upper respiratory infections, the peripheral white cell count varied from 27,000 per cubic millimeter to 141,000 per cubic millimeter, with immature myeloid cells always present. Occasionally, there were showers of monocytes, their percentage reaching 29 at one time. These monocytes were not normal, but many primitive, large monocytoid cells with indented eccentric nuclei were seen, such as described by Giffin and Watkins [38] (Fig. 14). Periodic increases in the number of these cells were encountered during the course of the disease, together with an identical fluctuation in the level of eosinophiles. During this period, the patient developed a mild anemia. The hemoglobin was maintained at moderately satisfactory levels by occasional blood transfusions. When x-ray radiations were instituted on April 4, 1950, and continued twice weekly until July 31, 1950, the white

blood cell count fell to 21,800 and the platelets from 270,000 per cubic millimeter to 80,000 per cubic millimeter. At the same time, the hemoglobin rose from 46% to 84% and the red blood cell count from 2,350,000 to 4,690,000 per cubic millimeter. The liver became smaller in size, and while its lower edge had reached the umbilicus before the start of the radiations, it could now be felt 1 fingerbreadth below the costal margin. The spleen also reduced considerably in size.

In the middle of October, 1950, there was again increasing hepatosplenomegaly, and both organs reached in January, 1951, the iliac crest on their respective sides.

In January, 1951, the hemoglobin was 57%; the total white cell count 111,000 per cubic millimeter, with a differential count showing 92% myeloid cells at the various levels of maturation from myeloblasts to polymorphonuclear leucocytes. There were 9 nucleated red blood cells seen per 100 white cells. The platelets were 60,000 per cubic millimeter. A second course of x-ray radiation was given between Jan. 19 and Feb. 23, 1951, to the abdomen and the anterior and posterior splenic areas. During this period, the liver and spleen increased slightly in size and the white blood cell count fluctuated between 60,000 and 174,000 per cubic millimeter. Because of lack of response after 432 r to the abdomen and 378 r to the splenic areas, this treatment was discontinued. The condition had become resistant to x-ray treatment.

In April, 1951, urethan therapy was begun. The drug was administered by enema because of nausea and vomiting when taken orally. Dosage levels of 20 grains (1.3 gm.) daily were achieved within a week. While the dose was maintained at this level for two weeks, the white cell counts rose from the range of 68,000 to 100,000 per cubic millimeter to 162,000 to 231,000 per cubic millimeter. The hemoglobin fell, necessitating two transfusions, and hepatosplenomegaly remained unchanged. Urethan was, therefore, considered ineffective although the period of trial was relatively short.

Triethylenemelamine was started orally on April 18, 1951, when it was given in doses of 2.5 mg. without discontinuing the daily dose of 20 grains of urethan. By giving both drugs simultaneously, it was hoped that a synergistic effect might be achieved, and smaller doses of both drugs could be employed. A second 2.5-mg. dose of triethylenemelamine was given four days later. Within a week following the second dose, the peripheral white cell count fell from 184,000 per cubic millimeter to 80,380 per cubic millimeter. The red blood cells were then 2,290,000 and the hemoglobin, 42%. A transfusion was given. A third dose of triethylenemelamine was given on May 1, 1951, and the white cell count decreased further to the neighborhood of 38,000. During this period, there was marked clinical improvement. There were no secondary infections, and the patient appeared cheerful. However, the liver and spleen remained unchanged in size. During the next six weeks three more 2.5-mg. doses of triethylenemelamine were given. The peripheral white blood cell count leveled off at 28,000 per cubic millimeter, and the hemoglobin remained around 50% without the aid of transfusion.

During the last four weeks, there was a considerable increase in erythropoietic activity in the bone marrow, which had become moderately less cellular and was now within the normal range quantitatively. The number of nucleated red cells in the peripheral smear was also strikingly increased and ranged between 49 and 86 per 100 white cells. During the last two weeks of the patient's life, the peripheral blood

showed a marked increase in monocytoid cells, and the bone marrow contained many monocytoid myelocytes and myeloblasts. If these blood and bone marrow changes had occurred in a patient not suffering from xanthomatosis, the diagnosis of a chronic myelogenous leukemia would have been justified.

In the presented case it had to be considered that leukemic phenomena developed during the course of systemic reticuloendotheliosis. The question arose whether there were two diseases present at the same time—xanthomatosis and leukemia—or one single condition produced by increased proliferative activity of the reticulum. The differentiation of the primitive mesenchymal cells into two directions, into the histiocyte—proved by the presence of innumerable undifferentiated foam cells and their argyrophilic reticulum, and into hematic elements—confirmed by extramedullary hematopoiesis and the leukemic blood and bone marrow picture, molds xanthomatosis and leukemic response into one pathological entity. A link is thereby established leading from the aleukemic forms of systemic reticuloendotheliosis to the leukemias. Fresen,[39] in his recent paper on the retothelial hemoblastoses, uses for cases where simultaneous systemic proliferation of myeloic and reticular cells is found the term "reticular myelosis." He stresses that the histology of this condition is identical with that of systemic reticuloendotheliosis.

One of the conspicuous findings in the presented case was the foamy undifferentiated embryonic stem cell. Deposits of primitive mesenchymal cells are significantly seen in the tissues of leukemic patients, due to heteroplastic blood formation, but cholesterol accumulation in these cells was never observed. This finding betrays the histiocytic orientation of these cells and presents the first and only instance where their development in a specific direction—the histiocyte—can be foreseen. This primitive foam cell is the progeny of the foamy histiocyte of the aleukemic type of this disease and, just as in these forms, is enmeshed in a dense argyrophilic reticulum (Fig. 15). This is in full agreement with the classic definition of reticuloendotheliosis by Tschistowisch and Bykowa,[40] who stated that this term should be reserved for cases with systemic proliferation of mononuclear cells conforming to the undifferentiated embryonic elements and who regarded the reticular structure as the most important diagnostic criterion.

There was marked pleomorphism throughout the areas of atypical reticulum proliferation, in contrast to the monotony and the more uniform cell types seen in leukemias. These findings are in conformance with the opinion of Sacks,[41] who stressed the importance of this disparity in these two conditions.

In xanthomatosis, there is a hyperplasia consisting of the formation of many cellular elements similar to the tissue from which they are derived. On the other hand, in leukemia or any other neoplastic growth, there are more or less atypical cells which fail to reach complete differentiation and retain, if any, only abnormal and perverted functional activity. In a case of xanthomatosis leading to the development of leukemic phenomena, the problem arose whether there was still only hyperplasia or whether this condition should be regarded as neoplasm. A clear-cut borderline cannot be drawn, and, indeed, it does not exist in nature. Fraser [42] suggested the reticuloses may provide a link between local tumor growth and systemic proliferative disease. Rohr [43] mentioned histological transition forms, where in a leukemia a proliferative response of the "reticulohistiocytic system" or in "malignant reticulosis"

a "myeloid metaplasia" exists simultaneously. Waugh [44] introduced the term kataplasia, which approaches on the one hand hyperplasia and on the other hand neoplastic growth; in this condition, the cells do not reach complete differentiation, often show atypical features of development, but still exhibit evidence of environmental control and lack of independence of neoplasms.

A new surprising finding was ascertained at autopsy—numerous inclusion bodies in all of the affected organs. The etiology of systemic reticuloendotheliosis is not known, but many authors, including Siwe,[45] expressed the opinion that there may be a causative infection—perhaps a virus. For this reason, the acute types of this condition were often classified as infectious reticuloendotheliosis. There are three reports in the literature in which antibiotic treatment was used successfully in systemic reticuloendotheliosis: Aronson and Lond [46] saw favorable results after the

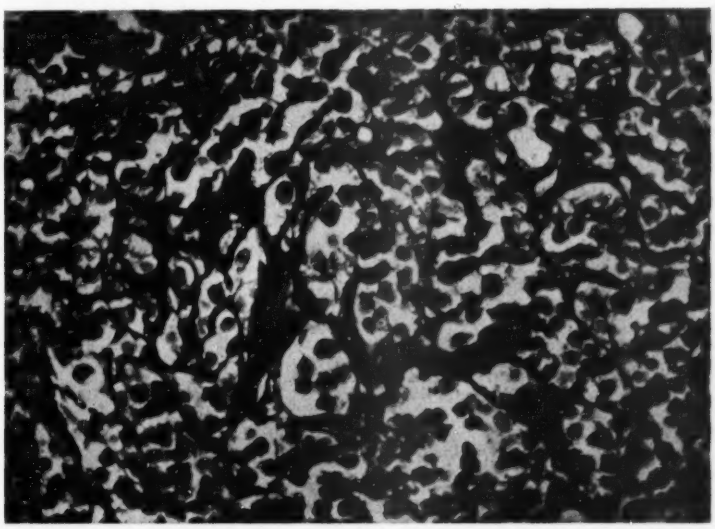


Fig. 15.—Lymph node, silver impregnation: dense argyrophilic reticulum (× 280).

administration of streptomycin; Bierman and co-workers [47] treated twins suffering from this condition with penicillin, streptomycin, chlortetracycline (Aureomycin), and chloramphenicol and observed the disappearance of hepatosplenomegaly and lymphadenopathy, healing of osteolytic lesions (x-ray controls), and regression of anemia. Fisher [48] reported a case with the typical findings of Letterer-Siwe disease, where cultures from blood and bone lesions revealed paracolon Arizona bacillus. His case responded favorably to antibiotics. These therapeutic results support the hypothesis of an infectious etiology. Of special interest is a case of Worth and Howard,[49] who observed an infant with the rapidly fatal form of this condition in which inclusion bodies were found in all organs and conspicuously in the adrenals, just as in our patient. Unfortunately, no virus studies were done because the inclusion bodies were only discovered at autopsy. A virus was probably the causative agent in their and our patients. However, inclusion-body disease or a superimposed virus infection cannot be excluded.

SUMMARY

A case of leukemic xanthomatosis has been described in detail.

Twenty-five months after xanthomatous skin lesions had appeared, the development of visceral reticuloendotheliosis could be detected in a lymph node.

A chronic leukemic myeloid response developed at the age of less than 2 years.

At autopsy, the lymph nodes, spleen, liver, lungs, and many other viscera were found to be affected by widespread reticuloendotheliosis.

There were many primitive mesenchymal foam cells with high cholesterol content, showing the histiocytic orientation of these cells, which were enmeshed in a dense argyrophilic reticulum.

The differentiation of the mesenchymal embryonic cells into histiocytes on the one hand and into hematic elements on the other seemed to establish a link between the aleukemic forms of systemic reticuloendotheliosis and the leukemias.

The problem whether leukemic xanthomatosis should be regarded as hyperplasia or neoplasm was discussed.

The possibility of the etiological significance of the inclusion bodies found in the tissues of this case was considered.

The pertaining literature was reviewed.

Dr. Siegfried J. Thannhauser, Dr. Paul Klemperer, and Dr. Sidney Farber gave advice in the preparation of this paper.

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SUBSTITUTION OF VINEGAR FOR LACTIC ACID AS BACTERICIDAL AGENT IN INFANT MILK MIXTURES

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BUTTERMILK was introduced as an infant food in Sweden in 1776, in Holland in 1865, in Germany in 1902, in France in 1907, and in the United States in 1913,* because it was found that infants thrived better on it than on ordinary sweet milk.[1] Other sour-milk mixtures soon followed. Clark and Faber attributed the value of the acid to an improvement in the digestibility of the milk.[4] They showed that the buffer value of cows' milk is considerably more than that of human milk, that it neutralizes a larger amount of the hydrochloric acid of the stomach, and thus may interfere with the activity of the gastric enzymes through a reduction of the gastric acidity below the optimal hydrogen-ion concentration zone of pH 3.5 to 5.0. The addition of an acid to cows' milk counteracted its excess buffer salts and made its digestibility more nearly that of human milk. Because of this and similar work,† many types of soured milk became popular for infant feeding in the United States. Lemon juice, citric acid, hydrochloric acid, and vinegar (acetic acid) have been used, but lactic acid milk has the widest use at present.‡

While it may be true that soured milk is more digestible than sweet milk[4] and that soft curds are important,§ the most likely reason that infants thrive better on soured milk and have fewer digestive upsets is the suggestion in 1927, by Marriott,[8] and the demonstration in 1935, by Rothey,[19] that milk containing 0.66% or more of lactic acid U. S. P. was bactericidal for dysentery, typhoid, and other organisms. Taylor and Roberts, in 1943, found that lactic acid milk could be left in open dishes at room temperature for three days before becoming contaminated by molds and for five days before bacteria appeared.[20] This bactericidal action has been clinically demonstrated at Duke Hospital for the past 20 years by the rarity of diarrhea and

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* References 1-3.

† References 5-11.

‡ References 1 and 12-14.

§ References 3, 15-18.

dysentery in infants fed lactic acid milk.|| The main disadvantages in using lactic acid are, first, that it is a poison if too strong a solution is used (30 cc. [1 fluidounce] of 85% lactic acid can be fatal),¶ and, second, that it is expensive.

Apple cider vinegar, which is cheap, nonpoisonous, and can be obtained at any grocery, is suggested in place of lactic acid. Apple cider vinegar contains 5 to 6% acetic acid, with variable traces of other harmless ingredients. Dunham, in 1925, fed various mixtures of apple vinegar and cows' milk to 40 infants over a period of one to six months.[24] The most satisfactory mixture was 30 cc. (1 oz.) of vinegar to 450 cc. (15 fluidounces) of cows' milk, or a final dilution of 6.66% of vinegar. The acetic acid content of this mixture is 0.33 to 0.40%. The general appearance, contentment, nutrition, tissue turgor, musculature, and rate of growth of these vinegar-milk-fed babies paralleled those of the infants fed lactic and citric acid mixtures. Their digestion was good; vomiting, flatulence, and refusal of the mixture were not encountered. The substitution of vinegar for the other acids did not noticeably change the clinical signs. The preparation of the vinegar-milk is similar to that of other acidified milk mixtures [25] (Appendix).

TABLE 1.—*Bactericidal Effect of Apple Cider Vinegar (Five to Six Per Cent Acetic Acid) on the Growth of Organisms Inoculated in an Infant Feeding Milk Mixture*

Milk Mixture, Cc.	Vinegar		Organism *				
	Amount, Cc.	Concentr., % †	S. dys.	S. parad.	S. typh.	S. parat.	Esch. coli
10.0	0 (control)	0 (0)	0	0	0	0	0
9.9	0.1	1 (0.05-0.06)	0	0	0	0	0
9.8	0.2	2 (0.1-0.12)	0	0	0	0	0
9.7	0.3	3 (0.15-0.18)	0	0	0	0	0
9.6	0.4	4 (0.2-0.24)	+	0	+	+	0
9.5	0.5	5 (0.25-0.3)	+	+	+	+	+

* S. dys. indicates Shigella dysenteriae; S. parad., Shigella paradysenteriae; S. typh., Salmonella typhosa; S. parat., Salmonella paratyphi B; Esch. coli., Escherichia coli; + indicates complete bactericidal effect, i. e., no viable bacteria.

† The first figures indicate the percentages of vinegar (5-6% acetic acid) and those in parentheses indicate the concentration of acetic acid.

Higher percentages of vinegar may exert an alkaline diuretic effect, but Sollmann fed massive doses to rats, equivalent in man to 240 cc. (8 fluidounces) of vinegar, daily for several months without any adverse effects. The addition of vinegar to the mash fed to young calves has reduced the incidence of scours (diarrhea).[26] A teaspoonful of apple cider vinegar (5 cc.) in a glass of water every four hours also is said to cure diarrhea in adults.[27]

The bactericidal effect of an increased acidity is well established. However, acetic and certain other organic acids appear to have a bactericidal effect in excess of that which could possibly be due to the pH alone. Kirby, in 1936, found that acetic acid or vinegar inhibited bread molds. At the same pH, greater inhibition was obtained with acetic acid. Collet, in 1919, found that in solutions of equal pH butyric and acetic acids were more bactericidal than hydrochloric and other strong acids. Levine concluded that organisms were inhibited or destroyed at a lower acidity when acetic acid was employed than when lactic or hydrochloric acids were

|| References 1 and 21.

¶ References 22 and 23 and Hartmann, A. F.: Personal communication to the authors.

used. Tchelenberg, in 1927, showed that alkali salts alone of several organic acids had no marked bactericidal effect. Vinegar has been used effectively for generations to preserve sauerkraut and pickles.

Bactericidal Effect of Apple Cider Vinegar (Acetic Acid) and Lactic Acid.—As indicated in Tables 1 and 2, 9.5 to 10 cc. of an infant-feeding milk mixture, comparable to the lactic acid mixtures used in our clinic (510 cc. [17 fluidounces] of water, 390 cc. [13 fluidounces] of evaporated milk, and 30 cc. [2 tablespoonfuls] of sugar [Appendix]) were transferred to two series of sterile test tubes to which 0 to 0.5 cc. of apple cider vinegar and lactic acid had been added, respectively, in amounts to produce total volumes of 10 cc. and acid concentrations of 0 (control) to 5%. Twenty-four-hour broth cultures of Shigella dysenteriae, Shigella paradysenteriae, Salmonella typhosa, Salmonella paratyphi, and Escherichia coli, in 0.1 cc. amounts, were added to each series of these tubes of acid milk, which were then

TABLE 2.—*Bactericidal Effect of U. S. P. Lactic Acid (Eighty-Five Per Cent Lactic Acid) on the Growth of Organisms Inoculated in an Infant Feeding Milk Mixture*

Milk Mixture, Cc.	Lactic Acid		Organism *				
	Amount, Cc.	Concentr., % †	S. dys.	S. parad.	S. typh.	S. parat.	Esch. coli
10.0	0 (control)		0	0	0	0	0
9.9	0.1	1 (0.85)	+	+	+	+	+
9.8	0.2	2 (1.7)	+	+	+	+	+
9.7	0.3	3 (2.55)	+	+	+	+	+
9.6	0.4	4 (3.4)	+	+	+	+	+
9.5	0.5	5 (4.25)	+	+	+	+	+

* S. dys. indicates Shigella dysenteriae; S. parad., Shigella paradysenteriae; S. typh., Salmonella typhosa; S. parat., Salmonella paratyphi B; Esch. coli., Escherichia coli; + indicates complete bactericidal effect, i. e., no viable bacteria.

† The first figures indicate the percentage of U. S. P. lactic acid (85%), and those in parentheses indicate the actual concentration of lactic acid.

incubated at 37.5 C. for 24 hours, streaked on eosin-methylene blue plates, and incubated for 48 hours. The presence or absence of growth on these plates (viable bacteria) is recorded in Tables 1 and 2.

CONCLUSIONS

1. Apple cider vinegar in a concentration of 4%, or 1 part of vinegar to 25 parts of an infant feeding milk mixture (0.2 to 0.24% acetic acid), prevents the growth of pathogenic bacteria.

2. Vinegar is a safe addition to milk to prevent pathogenic contamination.

3. Unlike lactic acid, vinegar is harmless in the proportions recommended.

4. Vinegar is easily obtainable and is cheap.

5. Vinegar milk is easily prepared, is palatable, and forms a soft smooth curd which flows easily through a nipple.

6. Infants thrive on vinegar milk (1 part of vinegar to 15 parts of cows' milk, i. e., 6.66% vinegar or 0.33 to 0.4% acetic acid).[24]

7. Vinegar milk retains all of the virtues of lactic acid milk,[1] but has none of its disadvantages and, in addition, is cheaper and easier to obtain.

APPENDIX

Home Instructions for the Preparation of Vinegar Evaporated Milk

Ingredients.—A 13-fluidounce can of unsweetened evaporated whole milk, 17 fluidounces water, 2 tablespoonfuls of sugar, and 3 tablespoonfuls of apple cider vinegar. The caloric content of this mixture is 22 Cal. per fluidounce. It can be used for normal infants from birth to 8 months of age. For older children, omit the sugar and reduce the calories to 20 per fluidounce.

Preparation.—Scald with boiling water a clean quart jar or milk bottle and an empty clean 13-fluidounce evaporated milk can. Fill this measuring can with water and pour it into the quart jar or milk bottle. Add 2 level standard tablespoonfuls of ordinary table sugar and 3 standard tablespoonfuls of ordinary apple cider vinegar to this water. As soon as the sugar has dissolved, cool this sugar and vinegar solution. Then open a 13-fluidounce can of unsweetened evaporated whole milk and pour the milk slowly into the quart jar or milk bottle containing the cold sugar and vinegar solution with continuous gentle shaking. Last, fill the quart jar or bottle of evaporated milk, water, sugar, and vinegar nearly to the top with cold water and reshake to make the mixture smooth. The mixture should not be boiled or pasteurized, as it will curdle. Refrigeration is unnecessary.[20]

If the water supply is bad or is well or pump water, the water should be boiled and cooled before using. A standard level tablespoon contains 12 gm. of sugar or 15 cc. of vinegar. Those obtained from several homes contained 7 to 16 gm. of sugar or 9 to 19 cc. of vinegar.# Ordinary table sugar is as good as Karo syrup or any other sugar. Chilling the sugar and vinegar solution facilitates mixing and makes a better curd. Do not pour the solution into the milk.

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FALLACY IN USING URINE TESTS AS INDICATORS OF ANTICONVULSANT DRUG TOXICITY

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THE REMARKABLE progress made in the control of epilepsy during the past five years has been due, in a large measure, to a handful of drugs with anticonvulsant action. Many of these drugs, such as trimethadione (Tridione)* and phenacemide (Phenurone), have potentially serious side-effects.† A few deaths have been attributed to trimethadione, phenacemide,‡ and Mesantoin.§ Dermatitis medicamentosa,[7] the nephrotic syndrome,‖ and bone marrow depression ¶ are the serious toxic reactions of these newer anticonvulsants. These have occurred more often when combined with the standard anticonvulsant preparations.# Judicious use, along with frequent clinical and laboratory observations during periods when the drugs are being used, should avoid serious complications in a high percentage of these patients.*

Recently, a report from England of the nephrotoxic effects of drugs used in the treatment of petit mal [19] suggested that even minor urinary changes occurring during the administration of trimethadione or paramethadione (Paradione) may indicate future serious renal damage. If these observations are correct, then it would seem that these extremely beneficial drugs must be used with greater caution than even now is customary. In view of the implications of this report, it seemed important to review the urinary findings over prolonged periods on some children who had received trimethadione or phenacemide.

MATERIALS AND METHODS

The records of 54 children, resident patients at the Emma Pendleton Bradley Home, a neuropsychiatric hospital for children, were reviewed for clinical or laboratory evidence of kidney damage. Of the entire group, six children had received

From the Emma Pendleton Bradley Home.
* References 2-4.
† References 1-3.
‡ References 4-6.
§ References 1 and 11.
‖ References 8-10.
¶ References 11-16.
# References 13 and 14.
* References 15-18.

trimethadione, while six others had received phenacemide, to control seizures. Sixteen children received *d*- or *l*-amphetamine for the organic syndrome of behavior, while 26 others had no regular medication for a prolonged period. The "amphetamine" and "no medication" groups were utilized for controls.

The children had been hospitalized for psychiatric rather than physical illnesses for a period varying from 1 to 29 months. They all received detailed laboratory studies on admission and at regular intervals thereafter. As a routine, any indication of physical illness was always followed with detailed clinical and laboratory examinations.

Urine values were classified as (1) normal: no albumin, red blood cells, or casts, (2) suspicious: albumin, trace to 1 + only, and (3) abnormal; albumin, 2 +, albumin 1 to 4+, and/or presence of red blood cells and/or casts, regardless of number per high power field.

The "suspicious" classification was so designated because a large number of children in the course of routine urinalysis, from time to time, have shown albumin, from a trace to 1+, without any other significant kidney abnormality.

TABLE 1.—*Incidence of Throat Cultures Positive for Hemolytic Streptococci Among Patients at Emma Pendleton Bradley Home*

No. studied	54
No. throat cultures positive for hemolytic Streptococcus	39 (72%)
At admission	27 (50%)
After admission	12 (22%)
No. throat cultures negative for hemolytic Streptococcus during hospitalization	15 (27%)

In July, 1953, a few cases of acute glomerulonephritis developed among the patients and the staff. It was then realized that since January, 1953, there had been an increasing number of throat cultures positive for hemolytic streptococci in the hospital. Since the relationship of the hemolytic streptococci to abnormal urine findings is well recognized, it is believed that this factor may contribute somewhat to the present study. Therefore, a survey of the throat culture findings in children presented in this study was made.

It was found that 39 (72%) of the 54 children studied had throat cultures positive for hemolytic streptococci sometime during their hospitalization (Table 1).

RESULTS

There were six children who received trimethadione for periods ranging from 5½ to 15 months (average, 10.9 months). An average of 21.3 urine specimens were studied at regular intervals. There was only one patient with abnormal urinary findings during the period he was given the medication.

Six other children received phenacemide for periods ranging from 5 to 12 months (average, 9 months). An average of 11 urine studies were made on these patients at regular intervals. There were three patients in this group with abnormal urinary findings.

Of the controls, there were 16 children who had been taking amphetamine for periods varying from 3 to 36 months (average, 16.6 months). An average of 9.5 urine examinations during the period of observation was made. There were seven children with abnormal urines.

There were 26 other children who received no regular medication over any prolonged period. These patients were observed for periods varying from 1 to 31 months (average, 14.2 months) and had an average of 8.9 urine specimens examined. There were 15 patients with abnormal urines (Table 2).

TABLE 2.—*Incidence of Patients with Abnormal Urine Specimens on Anticonvulsant Medication Trimethadione (Tridione) or Phenacemide (Phenurone) Compared with a Control Group*

Groups	No. Cases	Average Period of Observation, Mo.	Average No. Urine Specimens Examined	No. with Abnormal Urines	% with Abnormal Urines
Trimethadione	6	10.9 (5½-15)	21.3 (6-40)	1	16
Phenacemide	6	9 (5-12)	11 (6-20)	3	50
Amphetamine	16	16.6 (3-36)	9.5 (3-18)	7	43
No medication	26	14.2 (1-31)	8.9 (2-20)	15	57

TABLE 3.—*Incidence of Patients with Only Consistently "Normal" Urine Specimens on Anticonvulsant Medication Trimethadione (Tridione) or Phenacemide (Phenurone) Compared with a Control Group*

Groups	No. Cases	Average Period of Observation, Mo.	Average No. Urine Specimens Examined	No. Consistently Normal Urines	% Consistently Normal Urines
Trimethadione	6	10.8 (5½-15)	9 (6-12)	3	50
Phenacemide	6	...	...	0	0
Amphetamine	16	9.0 (3-15)	5.5 (3-8)	4	25
No medication	26	9.1 (1-18)	5.5 (2-13)	6	23

TABLE 4.—*Relationship of Throat Cultures Positive for Hemolytic Streptococcus to Incidence of Abnormal Urines*

	Throat Culture for Hemolytic Streptococcus—Positive				Throat Culture for Hemolytic Streptococcus—Negative			
Groups	No. Cases	No. with Normal Urines	No. with Abnormal Urines	% with Abnormal Urines	No. Cases	No. with Normal Urines	No. with Abnormal Urines	% with Abnormal Urines
Phenacemide (Phenurone)	2	1	1	50	4	2	2	50
Amphetamine	4	2	2	50	12	9	3	25
No medication	11	4	7	63	15	10	5	33

In a reverse procedure, children with "suspicious" and "abnormal" urines were excluded, and the number of children who had only consistently "normal" urines was ascertained. This finding occurred in half of those who received trimethadione, but in none who were taking phenacemide. In the control groups, completely normal urines occurred in approximately one-quarter of the cases. The control group had fewer urine specimens examined over an average shorter period than the groups on anticonvulsants (Table 3).

Hemolytic Streptococcus.—The possible relationship of the hemolytic streptococci in the throat to abnormal urines was evaluated. There seemed to be no relationship in the groups receiving anticonvulsant therapy. On the other hand, there were twice as many patients with abnormal urines in the control group with positive throat cultures as in those with negative cultures (Table 4).

COMMENT

This report was stimulated directly by the studies of Millichap and Kirman,[19] who concluded that microscopic urinary abnormalities were not uncommon with trimethadione therapy and that if such abnormalities were permitted to go unrecognized, they might lead to more serious kidney sequelae. It seemed important, therefore, to investigate possible side-actions of newer anticonvulsants, since they are being utilized in ever-increasing degrees.

In our hospital, little attention has been paid to minor urinary deviations in random samples, since it was a general feeling that this was a normal finding. The particular set-up of the Emma Pendleton Bradley Home is ideal for investigating a problem like this and determining whether or not our impression was incorrect. The children here are physically healthy and are hospitalized for long periods, during which they receive a multiplicity of laboratory studies at regularly scheduled intervals. This is exemplified by the average time and number of urine samples studied, as illustrated in Table 2.

This study shows that healthy children, receiving no medication, had the highest incidence of abnormal urines. Also, there seemed to be a significant relationship between the incidence of throat cultures positive for hemolytic streptococci and abnormal urines. Moreover, 50% of the entire patient population had positive throat cultures on admission, and an additional 22% developed this finding after hospitalization. Therefore, it seems more likely that mildly abnormal urine samples found at random may be related to bacterial sensitization rather than to specific chemotherapy.

Phenacemide was associated with a larger number of abnormal urine specimens than trimethadione. However, more detailed study of this group revealed that there were only two patients receiving this drug who started therapy with completely normal urines. Actually, one patient had evidence of glomerulonephritis prior to taking phenacemide. Detailed studies while he was receiving this medication failed to show evidence of increasing renal impairment. Another child reported in this study received trimethadione for several months during a first hospital admission, in 1949, and had several "suspicious" urines. On a subsequent hospital admission two and one-half years later, he had normal urines. When given phenacemide, he developed a few "suspicious" samples during a nine-month period.

The study shows clearly that if children who are not receiving anticonvulsants are followed carefully with repeat urinary studies over a long time, minor urinary abnormalities are common. They are seen to be as common as, or more frequent than, those reported in children who are receiving anticonvulsants. Thus, these minor urinary abnormalities do not really warrant in themselves the statement that they are indicative of kidney damage attributable to the use of the newer antiepileptic medications.

SUMMARY AND CONCLUSIONS

There was no evidence that trimethadione (Tridione) or phenacemide (Phenurone) had a serious nephrotoxic effect on the children studied or that an occasional abnormal urine was related to anticonvulsant therapy alone.

An occasional abnormal urine was a common finding in healthy children studied for long periods. The finding could be related to sensitization by hemolytic streptococci.

Minor urinary abnormalities in themselves are not indicative of kidney damage.

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INABSORBABILITY OF BORIC ACID IN INFANT POWDER

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IN RECENT years, considerable attention has been directed to the dangers and hazards incident to the misuse of boric acid.* This, of course, has been very rightly inspired by the regrettable reports of accidental deaths, especially in small infants. It is unfortunate, however, that it has not been made clear either to the public or the profession that all reported cases have been due to the accidental, ignorant, and at times negligent application or ingestion of saturated solutions of boric acid, undiluted boric acid powder, or powders and ointments containing high concentrations of boric acid. No cases of local or systemic toxicity have been reported, for example, from the use of standard baby powders, most of which contain boric acid in concentrations up to 5%. These preparations, carefully tested and manufactured by ethical firms, have been safely used and are continuing to be used on countless thousands of infants without untoward effects. None the less, the justifiable campaign against certain forms of boric acid preparations which are potentially toxic has been permitted to merge into an unjustifiable campaign against all products containing boric acid. This, of course, is an *argumentum ad absurdum*, since, if we were to eliminate all products containing boron or its compounds, we would eliminate from our dietary a host of foodstuffs such as lamb, fish, crabs, lobsters, mussels, chicken, and eggs.† Boron is also present in appreciable amounts in cereals because of the common, and in some cases essential, use of borax in fertilizers. We are in total agreement with Kleiner [14] who has stated:

> In the deplorable instances in which fatalities occur because of human error, as it unfortunately happens from time to time, the blame should be placed where it unquestionably belongs. To raise the cry of poison in connection with the mistakenly applied substance is an unworthy attempt to shift responsibility from man to matter, a wholly illogical and palpably misleading strategem which brings no credit to the profession.

Boron and the boron compounds were subjected to very intensive scientific study in the first 30 to 40 years of the century. In the early days of canning foodstuffs, the possibility of using boric acid as a preservative was discussed throughout scientific circles.[15] Modern methods of canning and refrigeration eliminated this consideration. Even up to the early forties, boric acid solutions and ointments were widely applied in the treatment of burns and wounds and in the irrigation of body

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* References 1-10.

† References 11-13.

cavities. The development of far superior antiseptics, bactericidal agents, and other methods of treatment obviously has made boric acid preparations in these fields superfluous. Boric acid was never an effective antiseptic, and no one at this time seriously considers its use as such. It has continued to be introduced in the manufacture of cosmetic powders chiefly because it is a practical and highly effective buffer. All talcs are alkaline and unbuffered might be irritative to the skin, particularly the skin of small infants. Hence, there are few powders on the market for infant or adult use which do not contain some boron, generally in the form of boric acid. The possibility that boric acid when used for this purpose might be absorbed in toxic amounts seems remote. However, since no observations have been recorded with respect to this possibility, and since the issue has been raised, albeit indirectly, it was thought advisable to conduct a series of studies that might perhaps resolve the problem.

METHODS

For the purpose of this study, it was necessary to analyze relatively small samples of blood and urine for boron in concentrations anticipated to be less than 30 ppm. The turmeric acid-paper-test method, commonly used, was not considered, since it frequently gives false positives and is unsuitable quantitatively.[16] A variety of other methods for assaying boron are available. Most of these procedures are based on the following techniques: (1) colorimetric methods, (2) spectrographic methods, (3) fluorescence measurements, and (4) identical pH titrations. While these methods are sufficiently accurate for soils and other organic materials, only the colorimetric method using carmine N. F. and carminic acid was found to give the required accuracy and reproductibility with biological samples of less than 5 ml. Accordingly, Smith and co-workers [17] confined themselves to a development of this method. Many technical problems were met and satisfactorily overcome by these workers before the procedure was considered accurate enough to apply to the clinical problem. One of these was the necessity of finding a method which would destroy the organic matter and at the same time prevent the loss of boron by volatilization. Four different techniques were tried before it was found that dry ashing with lithium carbonate at 650 C. was the best method of destroying the organic matter and preserving the boron. Another problem was encountered in the preparation of standard curves for blood and urine. This required that the blood and urine used be boron-free before the addition of known values of boron. While some blood samples could be found to be boron-free when checked spectrographically, this was never possible with the normal urine samples used, which were always found to contain traces of boron. Urine samples for this purpose were finally rendered boron-free by the Chapin [18] distillation method and then used to prepare standards.

To check the accuracy and precision of the method, samples of rabbit blood, human blood, and human urine were made up with known concentrations of boron in the range of 1 to 10 ppm.

The following tabulation summarizes the result:

	Human Blood	Rabbit Blood	Human Urine
Number of tests	22	23	30
Per cent recovery	101	101	100
Standard deviation (ppm)	0.31	0.28	0.45

After the above results were determined, a series of experiments was performed to establish the upper limit of the method. Satisfactory results were obtained with boron concentrations as high as 3 mg. per 100 cc. For optimum accuracy, however, it was found better to reduce the sample size and the size of the control when the boron concentrations exceeded 1 mg. per 100 cc. For the actual determination, 2 ml. aliquots of blood or urine were used.

It should be noted that the glass utilized in the boron assays, as well as that used for the collection of specimens, was especially prepared by the Corning Glass Works, of Olean, N. Y., and was warranted boron-free.

CLINICAL PLAN

Infants in residence at the New York Foundling Hospital were the source of the clinical material. This hospital is a multifunctioning institution with a census of approximately 250 infants from birth to 2 years of age. The majority of the infants are under one year of age, and are either dependent, abandoned, or neglected infants, awaiting social disposition. The average institutional stay is about three months, although discharges may occur before that time. This makes it rather difficult to engage in long-term studies, especially since our policy is to allow nothing to interfere with social disposition. In order to circumvent the possibility of inadequate case material, many more infants were incorporated in the study plan than would have been necessary had we been able to stabilize the census. Two of the nine floors of the institution, housing approximately 85 well infants, were selected for the investigation. Most of these infants were under 6 months of age, although a few (six) on whom determinations were made were somewhat older. All the infants on these floors were placed on the same regimen, so that blood and urine samples could be obtained from any of them. For practical purposes, therefore, these infants served as a "pool" for the collection of specimens.

As a preliminary to the study, carefully weighed individual containers of baby powder were distributed to 25 infants.‡ An experienced nurse was then instructed to give each of these infants a single routine application of powder after a diaper change and to return the container. The nurse was not informed as to the purpose of this procedure. After all the containers were returned, they were again carefully weighed, and it was determined that the average amount of powder used at each diaper change was 0.894 gm. per kilogram of body weight, with a range from 0.404 to 1.342 gm. Laundry studies and repeated counts on the two floors indicated that each infant underwent 7 to 10 diaper changes in 24 hours. Allowing for the maximum of 10 diaper changes, it could be assumed that each infant was exposed to at least 8.64 gm. of powder per kilogram of body weight daily.

The clinical study was divided into two parts, a control period and a test period, and was continued for about seven months.

During the control period, all powders, lotions, etc., were removed from the floors, and the nurses were instructed to use only soap and water for care of the buttocks. After this regimen had been in effect for a minimum of one month, the collection of blood and urine specimens was begun. Approximately 5 ml. of blood

‡ The product used throughout the study was Johnson & Johnson's Baby Powder, which was checked by assay and found to contain 5% boric acid.

was obtained under sterile conditions, using boron-free sodium citrate as an anticoagulant, and placed in the boron-free glass tubes previously mentioned, sealed with wax, labeled with the name and hospital number of the patient, and immediately submitted to the laboratory for assay. No other information was submitted to the assayists. Urine specimens of about 10 ml. in volume were handled in the same manner. Whenever possible, efforts were made to collect blood and urine samples from the same infant on the same day. In addition to the fact that all the control infants had been on the soap and water regimen for at least one month, it should be noted that none of the infants selected as controls suffered from any skin pathology.

TABLE 1.—*Controls* *

Case No.	Age, Mo.	Sex	Race	Weight, Gm.	Blood Assays		Urine Assays	
					Date	Results Mg./ 100 Cc.	Date	Results Mg./ 100 Cc.
1	5	F	W	5,240	10/16/52	0.09	10/16/52	0.03
							10/22/52	0.04
2	4	M	W	5,780	10/16/52	0.04	10/16/52	0.21
				6,060	11/ 4/52	0.11	10/26/52	0.13
							10/30/52	0.26
3	2½	M	W	5,610	10/16/52	0.12	10/16/52	0.26
				5,670	11/ 4/52	0.17	10/22/52	0.05
							10/26/52	0.07
4	2½	M	W	.....	10/18/52	0.06	10/18/52	0.04
							10/26/52	0.07
					11/ 4/52	0.17	11/ 4/52	0.12
5	2	M	W	5,240	10/16/52	0.05	10/18/52	0.04
				5,690	11/ 4/52	0.00	10/29/52	0.00
6	2	M	W	4,870	10/18/52	0.06	10/18/52	0.04
7	4	M	W	4,730	10/22/52	0.10	10/22/52	0.00
							10/30/52	0.02
				5,100	11/ 5/52	0.11	11/ 5/52	0.04
8	3	M	W	5,410	10/22/52	0.07	10/22/52	0.05
9	2	M	W	4,470	10/22/52	0.09	10/22/52	0.00
							10/29/52	0.09
				4,640	11/ 5/52	0.10	11/ 5/52	0.06
10	2½	F	W	5,100	10/22/52	0.08	10/22/52	0.05
				5,330			10/29/52	0.05
							11/15/52	0.03
11	5	F	W	5,780	10/22/52	0.08	10/22/52	0.09
							10/29/52	0.02
				6,030	11/ 5/52	0.09	11/ 5/52	0.03
12	4½	F	W	6,010	10/22/52	0.09	10/22/52	0.04
				6,260	11/ 5/52	0.19	11/ 5/52	0.16
13	4	M	N	6,800			10/29/52	0.30
				6,910	11/ 5/52	0.15	11/ 5/52	0.26

* No powder was used for a minimum of at least one month before samples were obtained.

Part II of this study served as the test period. At this time, the routine for care of the buttocks on the two study floors was changed in one particular; the nurses were instructed to apply powder with each diaper change. After this routine had been in effect for one month, the collection of specimens was again undertaken.

The infants during the test period were divided into three groups. Group A consisted of those whose integument was clean and who had been on the powder routine for at least one month. Blood and urine samples were obtained from this group. As the work progressed with this group, it was noted that the urine collections were exceeding the blood samples in number. This was due, of course, to the much greater ease with which urine samples could be secured. Therefore, in order to augment the number of blood samples, Group B was established. These infants met all the criteria of Group A infants, but from them only blood samples were

drawn. Group C was comprised of infants who developed rashes of varying nature and intensity during the course of the test period. They were continued on the powder regimen, and blood samples were collected 48 to 72 hours after the rashes had appeared.

RESULTS

Table 1 depicts the boron values obtained in the first period of the study, during which time no powder had been used on the infants for at least one month. The concentration of boron in the blood of the controls ranged from 0.0 to 0.19 mg. per 100 cc. In the urines, the values obtained varied from 0.0 to 0.3 mg. per 100 cc.

TABLE 2.—*Test Group A*

Case No.	Age, Mo.	Sex	Race	Weight, Gm.	Approx. Amt. Powder Daily, Gm.	Approx. Amt. Boric Acid Exposure Daily, Gm.	Blood Assays		Urine Assays	
							Date	Mg./ 100 Cc.	Date	Mg./ 100 Cc.
1	5	M	W	6,530	56.42	2.82	12/18/52	0.05	12/18/52	0.09
									12/28/52	0.27
									1/ 7/53	0.18
									1/14/53	0.13
2	7	M	N	6,740	58.23	2.91	12/18/52	0.04	12/18/52	0.08
									12/28/52	0.29
									1/ 6/53	0.18
									1/14/53	0.09
3	2	M	W	5,130	44.32	2.2	.....	....	12/18/52	0.03
4	4	M	N	5,100	44.06	2.2	12/18/52	0.08	12/18/52	0.02
									12/28/52	0.02
									1/ 7/53	0.20
									1/14/53	0.04
5	3	M	W	4,900	42.33	2.1	.....	....	12/18/52	0.06
6	10	M	N	9,930	85.80	4.3	12/18/52	0.04	12/18/52	0.09
									12/28/52	0.05
7	2½	M	W	5,340	46.14	2.3	12/21/52	0.01	12/21/52	0.10
									12/28/52	0.23
8	4½	M	W	6,030	52.10	2.6	12/21/52	0.15	12/21/52	0.05
									12/28/52	0.19
									1/ 7/53	0.10
							1/14/53	0.08	1/14/53	0.09
9	3	F	W	4,730	39.87	1.99	12/21/52	0.01	12/21/52	0.53
									12/28/52	0.11
									1/ 7/53	0.35
									1/14/53	0.44
10	8	F	W	7,300	63.07	3.2	12/21/52	0.01	12/21/52	0.31
									12/28/52	0.36
									1/ 6/53	0.20
							1/14/53	0.06	1/14/53	0.99
11	8	M	W	7,760	67.05	3.4	12/21/52	0.12	12/21/52	0.44
									12/28/52	0.11
									1/ 6/53	0.02
							1/14/53	0.00	1/14/53	0.06
12	8½	M	W	7,600	65.66	3.28	12/12/52	0.14	12/21/52	0.11
									12/28/52	0.10
									1/ 6/53	0.14

Tables 2, 3, and 4 represent the boron assays on the Test Groups A, B, and C. It will be observed that we have also included in these tables the approximate amount of daily exposure to boric acid. It was previously pointed out that a single diaper change required an average of 0.864 gm. of powder per kilogram of body weight and that the infants underwent a maximum of 10 diaper changes daily. Each infant, therefore, could be presumed to utilize approximately 8.64 gm. of powder per kilogram of body weight. All of the powder used in the study was assayed and was found to contain 5% of boric acid; hence, 5% of the total amount of powder used daily represents the approximate amount of boric acid exposure per day. This

was mostly in the form of calcium and magnesium salts. On the basis of these figures, it was calculated that the infants were exposed to an average of 2.33 gm. of boric acid daily, with a range of between 1.7 and 4.3 gm.

TABLE 3.—*Test Group B*

Case No.	Age, Mo.	Sex	Race	Weight, Gm.	Approx. Amt. Powder Daily, Gm.	Approx. Amt. Boric Acid Exposure Daily, Gm.	Blood Assays	
							Date	Mg./ 100 Cc.
13	4½	M	N	5,860	50.63	2.5	3/ 6/53	0.03
14	4½	F	W	6,120	52.88	2.6	3/ 6/53	0.03
15	3½	F	W	5,470	47.26	2.4	3/ 6/53	0.03
16	4½	F	W	5,550	47.95	2.4	3/ 6/53	0.02
17	3½	M	W	5,040	43.55	2.2	3/ 6/53	0.02
18	4	M	W	5,930	51.24	2.6	3/ 6/53	0.02
19	4	F	N	5,590	48.30	2.4	3/16/53	0.05
20	3½	M	W	4,190	36.20	1.8	3/16/53	0.02
21	8	F	N	6,010	51.93	2.6	3/16/53	0.01
22	4½	M	W	4,640	40.09	2.0	3/16/53	0.02
23	4	F	W	6,320	54.60	2.7	3/31/53	0.05
24	4	F	W	6,180	53.40	2.7	3/16/53	0.01
25	5	M	W	7,700	66.53	3.3	3/31/53	0.06
26	6	M	W	7,330	63.33	3.2	3/31/53	0.06
27	4	M	W	5,920	51.15	2.6	3/31/53	0.04
28	3	F	W	6,350	54.86	2.7	3/31/53	0.03
29	3	F	W	4,930	42.60	2.1	3/31/53	0.05

TABLE 4.—*Test Group C*

Case No.	Age, Mo.	Sex	Race	Weight, Gm.	Approx. Amt. Powder Daily, Gm.	Approx. Amt. Boric Acid Exposure Daily, Gm.	Blood Assays		Condition of Skin
							Date	Mg./ 100 Cc.	
1	1½	M	W	3,940	34.04	1.7	1/27/53	0.06	Mod. S.D.R.*
							1/31/53	0.04	
2	1½	M	W	4,420	38.19	1.9	1/29/53	0.02	Mild D.R.†
3	1½	M	W	4,960	42.85	2.1	1/27/53	0.02	Mod. S.D.R.
4	1¼	M	W	4,450	38.45	1.9	1/27/53	0.15	Mod. S.D.R.
5	2	F	W	5,330	46.05	2.3	4/17/53	0.02	Mild D.R.
6	8½	M	W	7,640	66.01	3.3	1/17/53	0.07	Modified measles
7	3½	M	W	4,080	35.25	1.8	4/17/53	0.02	Mild D.R.
8	2	F	W	4,730	40.87	2.04	4/17/53	0.00	Mild D.R.
9	4	M	W	6,030	52.10	2.6	4/17/53	0.02	Mod. S.D.R.
10	2	F	W	4,390	37.93	1.9	4/17/53	0.00	Mild D.R.
11	2½	F	W	4,590	39.66	2.0	4/17/53	0.00	Mild D.R.
12	3	M	W	4,530	39.14	2.0	4/17/53	0.00	Mild D.R.

* Mod. S.D.R. indicates moderately severe diaper rash (erythema on buttocks, thigh, and lower abdomen).
† Mild D.R. indicates mild diaper rash (erythema on buttocks).

The urine assays of Test Group A, shown in Table 2, ranged from 0.02 mg. to 0.44 mg. per 100 cc. The blood values of Test Groups A and B (Tables 2 and 3) for boron varied from 0.01 mg. to 0.14 mg. per 100 cc.

Some interesting values were obtained from the blood assays of the Group C infants (Table 4), who developed rashes of various types during the test period. Four of these infants gave negative values, and the highest value obtained was 0.15 mg. per 100 cc.

Table 5 is a summary of all the assays, and gives the averages for the controls and test groups, as well as the standard deviation.

Since boric acid is rapidly excreted in the urine, higher values might have been obtained from the urine specimens if 24-hour samples had been analyzed or if urine specimens had been collected within one hour of powder application.§ This was obviously not practicable with small infants, and, moreover, we were interested in the cumulative effect in the blood, since we considered that this would be more significant from the point of view of potential toxicity.

COMMENT

It is apparent from the results obtained that only minute amounts of boron penetrated the skin of the infants in the test group, including those in Test Group C, who had developed various types of dermatitis in the course of the study. In fact, the results obtained in both the control and test groups fall close to the normal values, which are, for blood, 0.04 to 0.09 mg. per 100 cc. and, for urine, 0.07 to 0.15 mg. per 100 cc. Since the test infants were exposed to at least an average of 2.33 gm. of boric acid daily for a number of weeks, the data reveal how poorly absorbed boric acid actually is when present in talc. The situation is different in regard to absorb-

TABLE 5.—*Summary of Assays*

	Blood, Mg./100 Cc.			Urine, Mg./100 Cc.	
	Controls	Test Groups A & B	Test Group C	Controls	Test Groups A & B
Total number assays	21	30	13	31	37
Averages	0.10	0.04	0.06	0.08	0.16
Standard deviation	±0.05	±0.04	±0.04	±0.07	±0.14

ability through the skin when one is dealing with either boric acid in solution or with pure boric acid powder, and particularly so if open skin lesions are present. Cases of poisoning have been reported when these agents were used on infants with skin lesions, but even in these cases, the amounts used have been large. Brooke and Boggs' fatal case, who had a severe excoriated diaper rash, was exposed to an estimated dose of 250 gm. of powdered boric acid daily for several days.[10] The boron content of the whole blood in this infant was 21 mg. per 100 cc. Watson's case of infantile eczema had been treated all over the body with a saturated solution of boric acid and, subsequently, for several days with 10% boric acid ointment.[4] Abramson reported the death of an infant whose severe diaper rash had been treated with powdered boric acid and 10% boric acid ointment.[7] The amounts used in this case were not given, but must have been large, since composite tissue studies gave a value of 26 mg. of boron in 50 gm. of tissue.

The greatest number of fatal cases due to boric acid poisoning have been brought about by the accidental ingestion of boric acid by newborn infants. Fifteen of these cases have occurred, and 11 are reported in the literature.‖ The amounts ingested were from 1 to 6 gm. Birch's case ingested a mixture of borated glycerin, honey, and sodium borate (borax) for several days; the exact amounts of each substance were not known.[2]

§ References 19 and 20.

‖ References 1, 6, and 8.

The explanation for the lack of absorption of boric acid in talc and the ready absorption of boric acid in solution lies in the fact that ionized forms are not transmitted through the skin as readily as undissociated molecules. This has been demonstrated with substances other than boric acid.[21] Boric acid, when mixed with talc and subsequently wetted, yields a much higher degree of dissociation, due to salt formation with the alkaline components of talc, than does boric acid in solution. Kahlenberg demonstrated that in a series of borates and boric acid solutions studied, boric acid possessed the property of passing through the skin in perceptible amounts but the salts did not.¶

The practical lesson to be learned from this discussion is that powdered boric acid should not be dispensed "over the counter" to the public, nor should preparations of boric acid in solution be permitted where any possibility of human error may enter into their administration. This does not mean that one should abandon the use of talcs which contain small amounts of boric acid in a nonabsorbable form, since there is no evidence whatsoever in the literature or in practice that such products are dangerous.

CONCLUSIONS

Under the conditions of this study, boric acid, when present in a 5% concentration in talc, is practically unabsorbed through the intact skin of infants, even though erythema may be present.

39-A Gramercy Park (Dr. Vignec).

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Case Reports

RECURRENT ACUTE THYROIDITIS

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ALTHOUGH the nonsuppurative forms of thyroiditis are rather well known and clearly recognized, acute suppurative thyroiditis is much less often encountered in either children or adults. The rarity of this condition is indicated by the fact the present case is the first such observed at the Babies and Childrens Hospital, Cleveland, since it opened, in 1932, and that Young [1] observed only four cases during a period when 2,900 thyroidectomies were performed.

In 1939, Greenfield and Curtis [2] reviewed the subject and reported a case that subsequently developed laboratory evidence of decreased thyroid function, as indicated by a rather crude measurement of the blood iodine content. A few other cases have been reported since.* Antibiotic therapy offers the possibility of specific treatment of this disease, and modern tests of thyroid function can be used to measure the effect of acute suppuration upon the ability of the gland to trap iodine and convert it to thyroid hormone. These aspects were investigated in the present case.

REPORT OF CASE

First Admission.—D.M. (UH 615-935), a 5-year-old Negro girl, was brought to the emergency ward on Sept. 3, 1951, because of swelling in her neck, which was noted after three days of fever and sore throat. The child was admitted to the hospital and found to be acutely ill; her temperature was 103.3 F., pulse rate, 120, and respiration rate, 24. The left lobe of the thyroid gland was enlarged, and there was local redness, heat, and tenderness in this region. The changes extended down into the thoracic cage but did not cross the midline. Fluctuation was not present. The remainder of the physical examination was not remarkable. The leucocyte count was 8,600 per cubic millimeter, with the following differential count: 50% segmented neutrophiles, 10% unsegmented neutrophiles, 31% lymphocytes, 2% monocytes, 1% eosinophiles, and 6% unidentified mononuclear cells. The urinalysis and serologic reactions were normal; the blood culture was sterile; a throat culture grew normal flora, and a nose culture grew Staphylococcus aureus. X-ray film studies revealed slight tracheal compression and deviation due to a left-sided soft tissue mass.

Treatment was begun with chlortetracycline (Aureomycin), 50 mg. per kilogram of body weight per day, and 300,000 units of aqueous penicillin procaine daily. For the next seven days the patient remained febrile and there was no apparent response to therapy; oxytetracycline (Terramycin) was substituted for the chlortetracycline at the same dose level. Twenty-four hours later the temperature was normal; however, the signs of inflammation in the thyroid gland subsided more gradually, and at the time of discharge, on the 12th hospital day, the left lobe was still indurated and somewhat enlarged. At the one-month follow-up visit, a small nodule was palpable in the area of previous inflammation, but at the two-months visit this had disappeared. At no time was there clinical evidence of hypothyroidism.

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* References 3 and 4.

Second Admission.—For 15 months following her discharge, the child remained entirely well. Three days before readmission on Dec. 11, 1952, fever, sore throat, and dysphagia were noted. A follicular tonsillar exudate and a slight redness and fullness of the anterior neck were found. Treatment on an outpatient basis was begun with a single 300,000-unit injection of aqueous penicillin procaine and meth-dia-mer-sulfonamides, 3.0 gm. per day. After three days of this regimen at home, her symptoms were found to be progressing, and she was readmitted to the hospital. At this time, she again appeared acutely ill; her temperature was 102.7 F., pulse rate 128, respiration rate 32, and blood pressure 108/78. The left lobe and isthmus of the thyroid gland were enlarged to four or five times their normal size, and heat, redness, swelling, induration, and tenderness were noted in this area. A resolving follicular tonsillar exudate was present; otherwise the physical examination was not remarkable. The leucocyte count was 19,000 per cubic millimeter, with 82% segmented neutrophiles, 2% unsegmented neutrophiles, and 16% lymphocytes. The corrected sedimentation rate was 48 mm. in one hour (Wintrobe), the serum cholesterol 134 mg. per 100 cc., and the alkaline phosphatase 3.4 units. A throat culture grew Pneumococcus, a hemolytic Streptococcus, and Neisseria catarrhalis. X-ray films again demonstrated tracheal deviation and compression due to a left-sided soft tissue mass, but these findings were less marked than on the previous admission.

Effect of a Single Injection of Thyrotropin in a Case of Recurrent Thyroiditis

	Thyroid Uptake, I^{131} *			PBI, γ/100 Cc.		
Time	Control	After TSH	Change	Control	After TSH	Change
During acute attack	12.9	19.4	+6.5	7.6	11.2	+3.6
6 mo. later	8.1	10.3	+2.2	7.6	12.4	+4.8

* Expressed as per cent of the administered tracer dose.

Treatment was begun with penicillin and oxytetracycline, in the same doses as on the previous admission. There was a prompt decrease in fever and in the extent of the local inflammation. On the fourth hospital day, definite fluctuation was found in the left lobe of the thyroid gland, and incision and drainage were performed. The purulent material obtained was sterile on routine cultures, and the histologic sections showed "organizing and acute suppurative inflammation, clinically, of the thyroid." By the 6th hospital day, the patient was afebrile, and on the 11th hospital day the drainage from the surgical wound had ceased, and the patient was discharged well. At follow-up visits four and six months later she has remained well without symptoms of hypothyroidism.

SPECIAL TESTS OF THYROID FUNCTION

Two thyroid-stimulating hormone tests[6] were performed; one during the height of the second episode of thyroiditis and another six months later. In brief, this test consists of obtaining a control serum protein-bound iodine level and a control measurement of the three-hour thyroidal uptake of a tracer dose of I^{131}, immediately after which a single intramuscular dose of 5 U. S. P. units of a relatively pure preparation of thyrotropin is given. The following day the protein-bound iodine and three-hour I^{131} uptake are again determined and the effect of the thyroid-stimulating hormone is evaluated by the change in these determinations.

The results obtained are summarized in the Table.

COMMENT

The response of both fever and local signs of inflammation to a combination of oxytetracycline and penicillin during both episodes of the acute thyroiditis suggests a bacterial etiology. It is possible that had antibiotic therapy been started earlier in

the course of the second episode, abscess formation and incision and drainage could have been avoided. One can only speculate as to why this patient had two attacks of an unusual disease, each involving the same area of the thyroid gland.

A marked rise in the protein-bound iodine level following the injection of thyrotropin was observed on both occasions that the thyroid-stimulating hormone test was performed. It is interesting that both the control levels were in the high normal range. During the first test, the normal initial thyroidal uptake of I^{131} was followed by a significant increase after the administration of thyroid-stimulating hormone, characteristic of normal thyroid function and reserve. The diminished rise in I^{131} uptake found in the second test suggested low thyroid reserve, but the good response of the protein-bound iodine ruled this out. Previous studies [5] have revealed that exposure to comparatively small amounts of iodine can alter the I^{131} response in this fashion, so it appears likely that this patient had probably had such an exposure without it being recalled.

The normal uptake of I^{131} before the administration of thyroid-stimulating hormone during the acute episode is in contrast to the findings of others in cases of diffuse or subacute thyroiditis in which the I^{131} uptake was reported to be abnormally low during the acute stage of the disease.†

SUMMARY

An unusual case of recurrent acute thyroiditis with suppuration, in which antibiotics were administered and tests of thyroid function and reserve were performed, is described; no indication of impairment of thyroid function could be demonstrated.

Dr. William McK. Jefferies and Dr. Samuel Spector assisted in the study of this patient and in the preparation of the manuscript.

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CONGENITAL TOXOPLASMOSIS

Report of Case with Cataract, "Atypical" Vasopressin-Sensitive Diabetes Insipidus, and Marked Eosinophilia

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CONGENITAL toxoplasmosis is being reported with increasing frequency and, in almost all cases, hydrocephalus or microcephalus, chorioretinitis, convulsions, and cerebral calcifications have been present.[1] We wish to report a case of a 6-week-old infant with cerebral calcifications, with the unusual findings of unilateral cataract, hypernatremia, "atypical" vasopressin-(Pitressin-) sensitive diabetes insipidus, and marked eosinophilia of the peripheral blood and bone marrow.

REPORT OF CASE

M. V. H. entered the Grace-New Haven Community Hospital on June 5, 1953, at the age of 5½ weeks, because of lethargy, anorexia, and failure to gain weight. He had been born at term of a 23-year-old Rh-positive white mother whose serologic reactions for syphilis were negative. Labor and delivery were uneventful, and the mother said that she had not had a minor illness during pregnancy. At birth, the child had appeared normal, weighed 7 lb. 4 oz. (3,290 gm.), was 20 in. (50.8 cm.) long, and had a head circumference of 13 in. (33 cm.). The umbilical cord had oozed for two days following birth, but the bleeding had been controlled when the umbilical tie was replaced with a clamp and vitamin K (5 mg. every two hours for two days) was given. Initial feedings with lactose were offered, but because of lethargy they were not taken well. Mild jaundice appeared on the second day but did not persist for more than a few days. During the five days in the hospital, the patient required two hypodermoclyses.

At home, he first appeared hungry, but chewed on the nipple instead of sucking, cried a great deal, and was irritable. At the age of 2 weeks, he weighed 7 lb. 11 oz. (3,490 gm.). At this time he developed several paronychia and became lethargic. The former cleared on penicillin therapy, but the lethargy persisted and became more marked, and his fluid intake decreased to 10 to 12 fluidounces (276 to 355 cc.) daily. His weight at 3 weeks of age had dropped to 7 lb. 8 oz. (3,400 gm.). His upper lip became swollen, and bleeding occurred at the frenulum. His appetite decreased still further, and dropper feedings were instituted. Local therapy with methylrosaniline chloride (gentian violet) and a detergent had no effect on the swollen lip and inflamed upper alveolar ridge.

At 4½ weeks of age, the child weighed only 7 lb. 4 oz. and had a swollen red upper alveolar ridge, a swollen upper lip, hepatosplenomegaly, and a narrow left palpebral fissure. During the next week he began to vomit three or four times a day. The vomiting sometimes was projectile and occurred during or immediately after the feeding. His bowel movements were normal. The fluid intake was 10 to 12 fluidounces daily, and the child urinated only five or six times a day. At the age of 5½ weeks, he was admitted to the hospital.

Family History.—The parents were in good health, except for a mild seasonal vasomotor rhinitis in the father and rheumatic fever in the mother in childhood. A 19-month-old sibling was in excellent health. There was no history of hereditary or congenital diseases in the family tree.

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The only family pet, a great Dane, had had no recent illness.

Physical Examination.—The temperature was 98.6 F., the pulse rate, 150, respirations, irregular, 20 to 40 per minute, the head circumference, 36 cm., the chest, 33 cm., the abdomen, 31 cm., the length, 53 cm., and the weight, 3,330 gm. The patient was poorly nourished, with diminished subcutaneous tissue. He was lethargic but had a vigorous cry on stimulation. The infant did not seem in contact with his surroundings and had no head control. He chewed on the nipple instead of sucking. The skin was pale, with no jaundice, and had fair turgor. The mouth was partially open at rest because of the swelling of the upper lip and the alveolar ridge. The head was symmetrical; the fontanelle measured 2 cm. by 2 cm. and was under normal tension. The eyes were examined by Dr. R. M. Fasanella, of the Department of Ophthalmology, who reported as follows: Right eye: "The cornea was clear, finger tension normal, and the chamber formed. There was a pupillary membrane present which was best seen with the +10 lens of the ophthalmoscope. The media was hazy, but a fairly distinct disc with choroidal pigmentation on the temporal side was seen. The disc was of normal color. The retina, macula and vessels were normal." Left eye: "The eye was of normal size, finger tension normal, and the chamber of medium depth. The pupil did not dilate completely. The cornea showed no deposits (K. P.). The pupil was irregular and bound down to the anterior lens capsule by solid portions of the iris. In the medial side of the lens a very thick opacity was noted. The rest of the lens was clear enough so that a red reflex could be seen on the temporal side. However, no details of the retina could be seen." The ears were normal, and no evidence of thrush was seen in the mouth. The heart and lungs were normal. The liver edge was firm and at the level of the umbilicus, and the spleen was 4 cm. below the left costal margin. No other organs or masses were palpated. The circumcision was well healed and the testes were descended. The deep tendon reflexes were physiologic and the Moro and Babinski reflexes were positive.

Laboratory Data.—Urinalysis: There was a trace of reducing substance, but no albumin, acetone, cells, or unusual crystals in the sediment. The specific gravity was 1.006. Subsequent urines did not contain any reducing substance. Blood cell count: The hemoglobin was 11.1 gm. per 100 cc., the white blood cells 23,600 per cubic millimeter, with 6% segmented and 6% nonsegmented neutrophiles, 45.5% lymphocytes, 29.5% eosinophiles, 10% monocytes, 2% metamyelocytes, 0.5% myelocytes, and 0.5% promyelocytes. The platelets were adequate, and the red cells showed a slight hypochromia, anisocytosis, poikilocytosis, and polychromasia.

The nose and throat cultures contained normal flora, and the blood culture was sterile.

The reactions to the serologic and tuberculin tests were negative.

The glucose tolerance and galactose tolerance tests were performed and normal results obtained.

The liver function tests were as follows: direct bilirubin, 0.12 mg. per 100 cc.; total bilirubin, 0.74 mg. per 100 cc.; cephalin flocculation, 0 in 24 hours and 2+ in 48 hours; thymol flocculation, 1+; thymol turbidity, 7.3 units; alkaline phosphatase, 11.8 units (Bodansky).

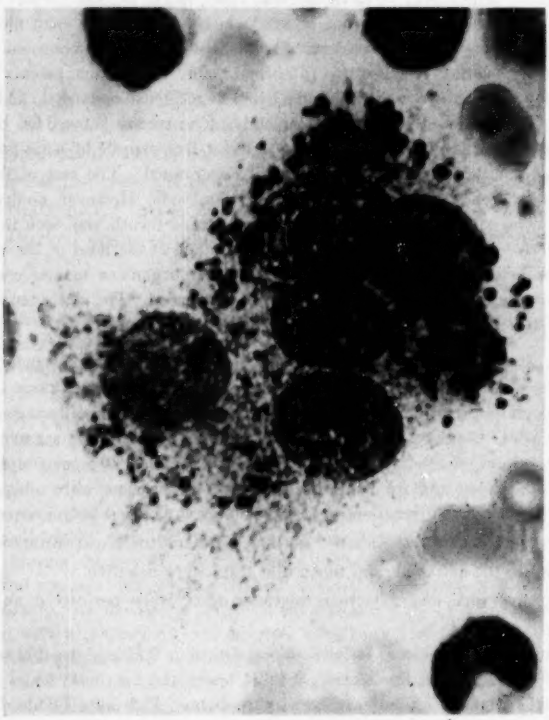
The differential count on bone marrow from the tibia was as follows: neutrophilic myelocytes, 2.5%; eosinophilic myelocytes, 1.5%; neutrophilic metamyelocytes, 29.5%; eosinophilic metamyelocytes, 8.5%; neutrophilic band forms, 22.0%; eosinophiles, 3.0%; lymphocytes, 15.5%; monocytes, 1.0%; pronormoblasts, 1.0%; normoblasts, 13.0%; normoblasts II, 2.0%; normoblasts III, 2.5%; blasts, 6.0%. The marrow also had several large multinucleated giant cells with one to three nucleoli in the nuclei and many deeply staining granules in the cytoplasm (Figure).

Lumbar Puncture.—The fluid obtained was xanthochromic and contained 13 WBC and 13 RBC per cubic millimeter and a protein content greater than 1,000 mg. per 100 cc. This fluid was injected intracerebrally into mice, but did not produce toxoplasmosis in the animals. No fluid was obtained from bilateral subdural taps. Roentgenograms of the chest and abdomen were normal, except for the presence of a large liver. The skull showed a fine flaky calcification symmetrically disposed in the cerebral hemispheres both anteriorly and posteriorly, but in greater density in the parieto-occipital region. There was also some calcification in the basal nuclei.

Serum was sent to the United States Public Health Service Laboratory in Chamblee, Ga., for study for toxoplasmosis. A titer of 1 : 4,096 on the patient's blood and 1 : 256 on the mother's blood was obtained by the dye test method.

Serum from the family's dog was tested by the dye method in the laboratory of Dr. D. Weinman II and was negative.

Antibiotic therapy consisting of sulfisoxazole (Gantrisin), 0.2 gm. per kilogram of body weight per day, and oxytetracycline (Terramycin), 50 mg. per kilogram per day, was instituted. Sulfisoxazole therapy was continued for 7 weeks, but oxytetracycline was discontinued after 11 days, when the diagnosis of toxoplasmosis was confirmed by the serologic findings.



Multinucleated giant cell from the bone marrow, containing many deeply staining granules in the cytoplasm.

The baby fed poorly during his early hospitalization, and by the fifth day showed signs of dehydration and a 200 gm. weight loss. At this time, the blood chemistries were as follows: nonprotein nitrogen, 60 mg. per 100 cc., serum sodium, 165 mEq. per liter, serum potassium, 5.3 mEq., serum chloride, 127.6 mEq. At the same time, the specific gravity of the urine was only 1.007. Over the following 48-hour period, an intravenous infusion of 800 cc. of 5% dextrose in water was given, along with oral feedings. The infant then appeared well-hydrated, and the blood chemistries were as follows: serum sodium, 146 mEq. per liter, and serum potassium, 4.0 mEq. Two days later, the infant again was dehydrated, and hyperelectrolytemia was again present. Throughout this time, the specific gravity of the urine remained at 1.007. The baby was given aqueous posterior pituitary extract (2 units every six hours for 24 hours). This produced a weight gain of 140 gm., and the serum sodium dropped from 160 to 144 mEq. per liter, with a drop of the serum potassium from 5.0 to 3.0 mEq. and a fall of the serum chloride

from 128.4 to 116 mEq. The carbon dioxide combining power remained at 22 mEq. per liter. The urine output in the 24-hour period that he was receiving vasopressin was only 30 cc. During the next four-day period, dehydration and hyperelectrolytemia recurred, but they again disappeared when the infant was given frequent small clyses of 5% glucose in water in addition to a half-skimmed milk formula. The baby's hydration was adequate on this regimen, until a period of hot humid weather resulted in the reappearance of evidences of dehydration. He then was given posterior pituitary powder intranasally three times daily, and this was successful in allowing him to maintain satisfactory hydration. Throughout the entire hospitalization, the infant had periods of subnormal temperature, which were most marked when the child seemed relatively well hydrated and had normal blood electrolytes. On several occasions, the body temperature dropped to 93.2 F.

One month after entry he still had an eosinophile count of 27.5%. He was discharged after eight and one-half weeks of hospitalization, weighing 3,875 gm.

The patient was seen two weeks after discharge and was progressing well on the intranasal posterior pituitary extract regimen. He weighed 4,600 gm., and his head circumference was 41.7 cm., a gain of 2.7 cm. in 16 days. A lumbar puncture showed clear slightly xanthochromic fluid, with a protein of 275 mg. per 100 cc. The blood chemistry values were as follows: carbon dioxide combining power, 23.4 mg. per 100 cc.; serum chloride, 115.6 mEq. per liter; serum sodium, 144 mEq.; serum potassium, 4.1 mEq.; N. P. N., 45.5 mg. per 100 cc.

At 4 months of age, word was received from the referring pediatrician that the patient died suddenly at home after a momentary cyanotic spell. Permission for a postmortem examination was refused.

COMMENT

Congenital toxoplasmosis probably occurs only when the mother acquires and transmits the infection during a rather limited period of pregnancy. Varying degrees of the disease may then become manifested at or before birth,[2] or their appearance may be delayed for weeks or months. In our patient, difficulties began within the first three weeks of life, and at no time subsequent to this did the child ever appear entirely normal.

From the reported cases, it would appear that congenital toxoplasmosis is a comparatively rare disease whose most common findings are chorioretinitis, cerebral calcifications, psychomotor retardation, hydrocephalus or microcephalus, and convulsive episodes. However, Sabin [3] has stated that

> countless millions of people in various parts of the world become infected with toxoplasma during their lifetime. If this be true, we cannot help but wonder whether clinically recognizable disease associated with such widespread infection is as rare as it now seems to be, or whether future awareness and intelligent application of appropriate diagnostic tests will supply us with clues to clinical syndromes of toxoplasmosis which are now lost in the vast mass of undiagnosable human disease.

In a study of 103 children with the disease, Feldman [4] found the commonest signs and symptoms of the congenital form to be chorioretinitis (99%), cerebral calcifications (63%), psychomotor retardation (56%), hydrocephalus or microcephalus (approximately 50%), and convulsive episodes (approximately 50%). However, it may be that these children had the more advanced stage of the disease, since Eichenwald * has stated that of about 75 infants with the congenital disease whom he has studied, only 40% had chorioretinitis at the time when they were first seen, although this percentage increased to about 80% when the survivors were examined subsequently.

* Personal communication to Feldman.[4]

In the eyes of our patient there were pupillary membranes bilaterally and a cataract involving part of the lens of one eye, which also had a congenital defect of the pupil. No evidence of chorioretinitis was noted. Cataracts have been reported previously by Gasser and Schwarz [5] and by Magnusson and Wahlgren.[6] Wilder [7] indicates that the cataracts which she found in the eyes of adult patients with apparent toxoplasmosis might have been a complication secondary to other eye changes.

Our patient showed persistent hypernatremia and an inability to concentrate the urine except on the administration of vasopressin injection. These findings are characteristic of certain cases of diabetes insipidus, but the infant differed from the typical example of the disease in that he had no polyuria or polydipsia. Ordinarily, thirst provides a safeguard against deficits of water, but it has been found that in a person with a clouded sensorium, large deficits of water can be present without the person complaining of thirst. In experimental animals, it has been noted [8] that considerable individual variations in the sensitivity of the thirst mechanism occurs and that the amount of water voluntarily ingested in response to hypertonicity is not entirely determined by the amount required to dilute injected salt to isotonicity. Similar individual differences in the sensitivity of the thirst mechanism in man might be found, but would not be expected to cause the pronounced disturbances found in our patient. Atypical diabetes insipidus has been reported by Engstrom and Liebman [9] in a patient who had a chronic hypernatremia, inability to concentrate the urine, some disturbance of memory and thinking processes, and a good response to vasopressin. In this woman, there was some defect in the thirst mechanism, which was manifested by the patient's voluntarily holding her fluid intake at a constant level, even when vasopressin was not being given and severe hypernatremia was present.

In our patient, the findings of vasopressin-sensitive diabetes insipidus, hypernatremia, and an absence of increased voluntary ingestion of water during periods when hypertonicity of body fluids was present may be explained by several theoretical mechanisms. First, there may be a deficiency of antidiuretic hormone in association with a thirst mechanism which might be fundamentally intact, but where the need for water was not expressed because of the clouded sensorium. Second, a neurologic lesion of the brain might have involved the area controlling the thirst mechanism, while another lesion resulted in the diabetes insipidus. Under these circumstances, even though the patient were conscious, there might be a very poor response to hypertonicity, and a chronic state of dehydration and hypernatremia would result. Finally, the toxoplasmosis may have involved an area of the brain which has direct nervous system control of the osmolarity of the intracellular and extracellular fluids. However, there has been no direct evidence to support this idea.

Hydrocephalus or microcephalus in toxoplasmosis is a variable and inconstant finding and, when it occurs, may be present at birth or may not appear for some time afterward. In our patient, changes in the size of the head were not evident until shortly before death, when some abnormal enlargement was noted for the first time.

Hypothermia was a recurrent and striking finding during the entire period of hospitalization and was most marked when the child appeared well hydrated and

had relatively normal blood chemistries. Although no definitive studies have been reported about a depression of the temperature in active toxoplasmosis, Frenkel and Friedlander [10] state that hypothermia is not infrequently associated with the encephalitis due to toxoplasmosis, and low body temperatures are mentioned as being present in some of the cases recorded in the literature.

Of particular interest was the finding of a 29.5% eosinophilia of the peripheral blood and an eosinophilia of 13% in the bone marrow. Eosinophilia has been reported many times in the literature † and seems to occur predominantly in two groups of patients. The first are children with widespread disease but with no involvement of the skin,‡ while the second group is made up of adults with a milder form of the disease § but in whom a generalized maculopapular eruption has been present.

Large multinucleated giant cells, with certain of the characteristics of osteoclasts and containing many deeply staining particles which could not be definitely identified but which were not characteristic of Toxoplasma, were found in the bone marrow. During the acute stage of the infection, several investigators have recovered organisms from the blood, bone marrow, splenic puncture material, cerebrospinal fluid, and, possibly, from the sputum.‖ Unfortunately, simultaneous animal inoculation studies were not carried out in our patient on the material aspirated from iliac crest, and so we cannot be certain as to the identity of these deeply staining particles.

The entire pathogenesis of toxoplasmosis has not been elucidated. The widespread involvement which was present when the child was first seen probably meant that he was in an early stage of the disease, since the early disease appears to be a generalized infection involving most organs. The relative disappearance of Toxoplasma and the regression and repair of lesions in the extraneural viscera with localization in neural structures has been explained on the basis of the developing of an acquired immunity, which is evidenced by fibrosis of lesions and by the mononuclear and eosinophile infiltration characteristic of repair, as well as by evidence of the development of serologic immunity.[10] Thus, the eosinophilia that we found may have been an indication that some regression and repair of the disease process had begun. Frenkel and Friedlander believe that the persistent proliferation of Toxoplasma in the neuroectoderm, after its almost complete disappearance from the extraneural viscera, may be dependent on the differential in antibody levels, since neuroectodermal tissues have many less antibodies than extraneural viscera.

Several alternative diagnoses were entertained when our patient entered the hospital. These included galactosemia, reticuloendotheliosis, cytomegalic inclusion-body disease, and widespread bacterial disease. In addition, one might consider various spirochetal and leptospiral diseases, Cryptococcus (Torula) and Coccidioides meningitis, subdural hematoma, various virus infections involving the fetus, and "degenerative" and hereditary diseases involving the retina, as well as the numerous causes of hydrocephalus and of cerebral calcifications (the latter includ-

† References 6 and 10-15.
‡ References 6, 10, and 11.
§ References 12-15.
‖ References 10 and 16.

ing Sturge-Weber syndrome, brain abscess, cysticercosis, trichinosis, tuberous sclerosis, parathyroid insufficiency, schistosomiasis, calcification of the pineal gland, the choroid plexus, the falx cerebri, or the petrosphenoid ligament, and various tumors).

Combined therapy with a sulfonamide and oxytetracycline produced an apparent temporary arrest in the disease process. In his review of therapy, Eyles [17] concludes that, although no chemotherapeutic agents now available have proved effective against human toxoplasmosis, there are a few drugs which can be used with the expectation of beneficial effect. The sulfonamides, particularly sulfadiazine and the closely related compounds sulfamethazine and sulfamerazine, are of value. He believes that the most promising recent development in the chemotherapy of toxoplasmosis was the discovery that the pyrimidine drug pyrimethamine (Daraprim) has a definite therapeutic effect against Toxoplasma and that this drug acts synergistically with the sulfonamides. Eyles believes that no other drugs could be recommended for the treatment of human toxoplasmosis. The antibiotics have only a slight effect, even at extremely high dosages, and none of the other groups so far investigated is outstandingly active. Perhaps the sulfones are an exception to this generalization. Sulfoxone (Diasone) and sodium glucosulfone (Promin) might be used with reasonable expectation of some effect, but most work would indicate that these are inferior to the better sulfonamides.

SUMMARY

A case of congenital toxoplasmosis in a 6-week-old infant with cataract, hyperelectrolytemia, "atypical" vasopressin-sensitive diabetes insipidus, and marked eosinophilia of the peripheral blood and bone marrow is presented.

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Progress in Pediatrics

MIGRAINE IN PEDIATRIC PRACTICE

Observations with Special Reference to Migraine of Allergic Origin

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BY THE term "migraine" is meant the periodic occurrence of headache, commonly unilateral, which may be associated with visual disturbances and/or a variety of other symptoms, and is usually accompanied or followed by nausea and vomiting. The mechanism of migraine is doubtless vascular in origin, as indicated by the original observations of Goltman [8] and Wolff.[28]

The frequency of the occurrence of migraine in pediatric practice has not been thoroughly documented. Riley,[20] of the New York City Neurological Institute, stated that this disease is not uncommon in children and noted eight patients at that clinic, varying in age from 8 to 13 years. Hecker,[11] in Germany, also stated that migraine in the early years of life is commoner than is generally supposed and observed 56 cases in a clinic which excluded children below the age of 6 years. Most of his patients were between the ages of 9 and 12 years. London,[14] in a study of the composition of the first 1,500 cases seen in an average pediatric practice, reported headache in 11 patients (migraine was not specified), an incidence of this symptom of about 1.4%. Balyeat and Rinkel,[2] in 1931, estimated that 7% of all the people in this country suffer from migraine at one time or another, that about 30% of these manifest symptoms before the age of 10 years, and that about 2% of all children manifest symptoms of migraine during the first decade. Vahlquist,[25] in Sweden, in 1951, also suggested an incidence of migraine of 7% in the general population and in Stockholm reported that 2% had typical attacks before the age of 6 years and 4 to 5% before the age of 11 to 12 years. Clein,[4] in 1945, reported an incidence of migraine of 2% in a series of 100 allergic children. In a more recent study of 516 allergic children, MacKinney and Glaser [15] noted that only 1.16% of these had migraine, which, curiously, was exactly the same as the percentage of children who had severe allergic reactions to insect bites. My findings, together with those of London cited above, indicate that the incidence of migraine in the pediatric population of this country is probably not significantly over 1%.

Balyeat and Brittain,[1] in a study of 55 patients with migraine, demonstrated that a hereditary factor was present in 85%. Michael and Williams [17] noted heredity as a factor in 15 of their 20 cases of migraine, an incidence of 75%. Vahlquist and Hackzell [26] noted that in 20 out of their 31 cases (67%) at least one of the parents or siblings had typical migraine, and in seven others the condition was present in one or more of the parents, siblings, or grandparents. These authors found an incidence of migraine in 13.3% in a control series of women whose average age was

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40 years, as compared with 38.7% in the mothers with the migrainous children under discussion. While they believe that heredity is a very strong factor in the development of migraine, they also found that in 26 families with severe migraine in one of the parents only 3 of 43 children (average age, 7 years) manifested signs of the same disease. Therefore, it would seem that migraine in one of the parents does not necessarily bring about early onset of the disease in the offspring.

According to Hecker,[11] twice as many boys as girls suffer from migraine. Vahlquist and Hackzell,[26] in a study of 31 patients whose onset of migraine was between the ages of 1 and 4 years, stated that about 23, or two-thirds, were boys. A greater incidence of males was found by Michael and Williams,[17] who studied 20 cases in children, ranging in age from 6 to 14 years, in whom onset varied from 2½ to 11 years. Of these, 13 were Negroes and 7 whites. There were 16 boys and 4 girls. In the series of 50 children reported by Krupp and Friedman,[13] there was no particular difference in the sex incidence. Ten successive cases in my practice were equally divided between boys and girls. Unger and Unger,[23] in a series of 55 patients with migraine, found that in 22 the onset was between the ages of 5 and 14 years. Of these, 5 were boys and 17 girls. One would conclude from the available data that there is no significant sex difference in those who suffer from this disease in childhood.

The age of onset of migraine in infancy and childhood is of considerable interest. The question, therefore, naturally arises as to how one can diagnose headache in infancy and early childhood. According to Plant,[18] in young infants headache may be suggested by wrinkling of the forehead, rubbing of the head, restlessness, and crying. The diagnosis appears to be established by observing the pattern of behavior which the infant or very young child exhibits during the attack. If, when the child grows older and can describe his symptoms, he complains of headache when exhibiting the same behavior pattern, it seems quite reasonable to suppose that headache was also present before he became old enough to complain about it.

Russell [21] reported a boy first studied at the age of 13 years who suffered from migraine and ophthalmoplegia; the evidence indicated that the attacks had started when the patient was only 2 weeks of age, probably the earliest onset on record.

Vahlquist and Hackzell [26] noted the case of a boy whose mother had menstrual migraine. This child's first attack occurred at the age of one year, when he suddenly turned pale and had an attack of vomiting. During the next two years, he had several attacks a week, always of the same type. When he was about 3 years of age, he began to complain of pain in his head during the attacks. Another case was that of a boy whose first attack started at the age of 2½ years. This consisted of a left-sided hemicrania, usually associated with nausea and sometimes vomiting, and, on one occasion, vertigo. The attacks generally occurred when he was tired or cold.

Balyeat and Rinkel [2] gave the protocols of three cases of patients, in one of whom migraine started at the age of 1½ years, and in the two others, at the age of 2 years. In the majority of Hecker's [11] cases, the illness began between the ages of 6 and 10 years. In one instance, however, the first attack occurred when the child was 1½ years of age, and in five between the ages of 2 and 3 years.

The youngest child I have ever seen with typical migraine was a girl of 3 years. She would act as though in pain, would pat one side of her head, and would constantly repeat the single word "hurt." These attacks were followed by abdominal

pain, nausea, and vomiting. However, the complaint for which the child was brought to the office was bronchial asthma, and migraine was elicited only in taking a detailed history. The few cases of migraine which I have seen in infants 5 years of age or less have all been diagnosed by careful history-taking, as the child was brought to the office for some other condition. That this state of affairs is not unusual is borne out by the observation of Balyeat and Rinkel [2] that at the time their article was written they had under their care a group of migrainous children under 5 years of age, all of whom came, not on account of headaches, but for relief of allergic syndromes.

It is generally agreed that the major symptoms of migraine in children and adults are very similar, but there are certain differences, as regards both the prodromal symptoms and the attacks. Balyeat and Rinkel [2] state that in children the prodromal symptoms are languor, loss of appetite, and abdominal discomfort, instead of the irritability and abnormal hunger which are so common in the adult. During the night preceding an attack, a patient may be abnormally restless or sleep abnormally soundly. The following morning, the temperature is often slightly elevated and may gradually rise to 104 F. (40 C.). Since this does not occur in the adult, the presence of fever may draw attention away from the diagnosis of migraine to an explanation of the subsequent abdominal pain, nausea, and vomiting as heralding the onset of an acute infection. Acute appendicitis may be suspected.[12] Other prodromal symptoms as noted by Riley [20] may be a sense of abdominal distention, vertigo, disturbance of the sense of smell, bad breath, and a very definite change in behavior, with sadness, excessive gaiety, or definite irritability. Cardiac symptoms may also be present, with the development of palpitation or bradycardia, pain, feeling of anxiety, shortness of breath, pallor, cyanosis, and sweating. Such cardiac symptoms have recently been described in adults by Briggs and Bellomo [3] as "precordial migraine." Intermittent edema, particularly of the face and eyelids, and, occasionally, periodic herpetic or bullous lesions may appear. The headache in young children may be minor at times but increases in severity with corresponding diminution of abdominal symptoms as the child gets older, the adult type of hemicrania being fully developed at about the age of 12 years. In my experience, also, the headache is less likely to be unilateral than is the case in adults, and scotomata occur less commonly.

None of the children reported by Riley [20] had hemianopsia, but fortification figures, scintillations, and scotomata were extremely vivid in some, and in one instance visual hallucinations of a terrifying character were present. In these, people appeared upside-down, and animals and objects with definite forms and characters made their appearance.

Hackzell and co-workers [10] have the impression that in children the prodromal symptoms of migraine, as well as the attacks, are of shorter duration and that nausea is more intense than in adults. Michael and Williams [17] state that the outstanding feature in children is the much greater frequency of the attacks. Two or three attacks a week were common, and in one patient the attacks occurred two or three times a day. Vahlquist and Hackzell [26] noted that most of the attacks lasted only a few hours, but in some instances, 12 to 48 hours. The average was about two and one-half hours. Attacks of headache were associated with nausea in all patients and culminated in vomiting in most of them. Frequently the attacks ranged from twice weekly to once quarterly.

In the differential diagnosis of the symptom complex of headache, abdominal pain, and emesis, one must consider the numerous possible causes of these symptoms.[19] Riley [20] stated that when a child presents abdominal symptoms of an obscure character careful investigation should be made into the past and family history in order to determine any tendency toward the development of migrainous episodes.

The psychogenic element appeared to Vahlquist and Hackzell [26] to be of major importance. The majority of the children were said by their parents to be sensitive, nervous, and of uneven disposition, with various behavior disturbances, such as nail-biting. Attacks were precipitated by such factors as nervous tension, insufficient sleep, irregular meals, fatigue, exposure to bright sunlight, and moving pictures. In view of the latter, it will be interesting to note the effect of television on these patients. Krupp and Friedman,[13] in 1953, reported a series of 50 children between the ages of 3 and 15 years and stated that practically all gave some evidence of psychogenic disturbance and recommended psychotherapeutic and symptomatic treatment. Allergy was not mentioned as a possible etiological factor.

The prognosis for migraine of early onset, according to Vahlquist and Hackzell,[26] did not appear to be especially unfavorable. The frequency of the attacks was said to be diminishing in 20 out of 22 patients who passed the age of 7 years. One of the patients, who was over 15 years of age, had been completely free from symptoms for seven years, and four of the others had at the most three or four attacks a year.

One of the commonest causes of recurrent headache in children, in my experience, has been errors of refraction, and this can cause the symptom complex of migraine. Grunert [9] stated that in 129 patients with migraine under the age of 15 years, he was able to relieve the symptoms by proper ophthalmological supervision. In my opinion, no child with headache should be given up as hopeless from the standpoint of relief other than by symptomatic remedies until he has been completely refracted by a truly competent oculist. I have had two children with diagnoses of migraine who obtained apparent cure by this procedure alone after the prolonged occlusion test of Marlow,[16] which is very time-consuming but in selected cases pays extremely rich dividends. In this connection, cyclic vomiting should be mentioned. This symptom complex, which has been observed by practically all students of the subject, notably Smith [22] and Vahlquist,[24] as an occasional precursor of migraine, is in some instances unquestionably due to food allergy.[5] However, the few cases of cyclic vomiting referred to me for study from the standpoint of allergy did not, in the instances where relief was obtained, receive this as a result of such studies but through the correction of errors of refraction.[6]

Another important cause of headache simulating migraine in allergic children may be the result of nasal congestion which obstructs the sinus ostia, producing, because of the absorption of air within the sinus, the so-called "vacuum headache." Occasionally headaches of this type may be easily diagnosed by relief following the use of vasoconstrictive nose drops.

It is, however, the purpose of this communication to call attention to the fact that some cases of migraine in childhood are due to food allergy. Although food has been known for many years as a cause of migraine, it was not until 1927 that Vaughn [27] reported on a series of controlled studies in adults which proved this point. Balyeat and Rinkel,[2] in 1931, drew attention to foods as a cause of migraine in childhood. Vahlquist and Hackzell,[26] in 1949, stated that, while some attacks of

migraine may be due to food allergy, their study does not bear out the theory that an allergic background is commonly found, at least in Sweden. In a subsequent study, Hackzell, Kraepelien, and Vahlquist [10] observed 40 persons with typical migraine from the standpoint of allergy. Skin tests gave positive results in 13 cases. Seven of these showed multiple, and in some cases strongly positive, reactions, for the most part to inhalant allergens. All seven had evidence of allergic disease. The incidence of typical allergic disease in the migraine patients themselves, as well as in their closest relatives, did not differ to any extent from that of a control series. Of the 20 cases of migraine studied by Michael and Williams,[17] in only 4 was there a family history of the usual types of allergy and in no case a personal history of allergy.

About the only conclusion that one can draw from the above evidence is that migraine may occur whether or not there is a past personal or family history of allergy. About the only importance that one can attach to a history of allergy in such circumstances is that when such a history is obtained it suggests that allergy is more likely to be a factor in the disease than when it is not obtained, but a negative history by no means rules out an allergic etiology.

Most of the children with migraine I have seen were brought in for consultation because of allergic difficulties, the migraine being elicited only in the course of the history-taking. In all instances in which the migraine could be proved to be due to food allergy, the offending foods were known by experience or were discovered, not by skin tests, but by means of elimination diets. Chocolate, wheat, milk, and eggs were the most frequent offenders. It seems reasonable to suppose that the allergens causing the attacks are intermediate metabolic products of these foods, the nature of which is unknown, and for which, therefore, no skin-testing materials are available. It must also be remembered that many instances of headache occur which are not typical migraine but which are of allergic origin. These patients may also be relieved, at times, by means of elimination diets.

Goltman [7] stated that while foods are of paramount importance as etiological factors in many cases of allergic origin in adults, as originally reported by Vaughn,[27] inhalants are the main factors. I have seen no reports of inhalant allergens as the cause of migraine in children, but that might be because inhalant factors as causes of migraine have not been given sufficient consideration in this age group. Unger and Unger [28] have concluded that chocolate is the commonest offending food, followed by milk, wheat, and pork. They stated that, although migraine is basically an allergic disease, psychic stimuli may produce attacks in allergic persons.

As regards the symptomatic treatment of migraine, ergotamine tartrate appears to give the best results. The dose is 1 mg. for a child of about 6 years of age with one-half a glass of water immediately at the onset of an attack and repeated in one hour if not relieved. Recently, suppositories of an ergotamine tartrate-caffeine preparation, which contains 2 mg. of ergotamine tartrate and 200 mg. of caffeine, have been reported upon favorably in adults by Zanfagna,[29] who recommended their use early after the onset of migraine in adults. I have had no experience with these in children, but presumably the dosage would be in proportion to the age and weight of the child.

Acetylsalicylic acid occasionally gives good relief, but it is sometimes necessary to use codeine or meperidine hydrochloride (Demerol). Phenobarbital, epinephrine,

ephedrine, the antihistaminics, and diphenylhydantoin (Dilantin) sodium have been of no significant help in my cases. It would seem reasonable that corticotropin (ACTH) or cortisone, if given at the very first aura of an attack, might be helpful in migraine of allergic origin, but acceptable studies concerning this have not yet been published.

The following case reports from my own practice illustrate childhood migraine of allergic origin.

REPORT OF CASES

CASE 1613.—A girl, 9 years of age, had cyclic vomiting as an infant, pollinosis at 5 years of age, and developed typical migraine at 9 years, the attacks occasionally being accompanied by fever. Her mother and maternal grandfather had suffered from migraine. Over a two-year period it was determined that the attacks commonly followed the ingestion of chocolate, and when this was removed from her diet migraine was no longer a problem.

CASE 3455.—In a boy who had frequent gastrointestinal disturbances during infancy, migraine developed at the age of 4 years and recurrent upper respiratory disorders of allergic origin as he grew older. At 13 years of age, the migraine became a serious problem. His father had migraine which was caused by milk. The boy was very fond of chocolate and in recent years had ingested chocolate with increasing frequency. On the omission of chocolate from the diet, the migraine largely ceased but could be precipitated by excitement, nervous strain, or fatigue.

CASE 4869.—A girl who had been studied at the age of 6 months for atopic dermatitis was not seen again until the age of 9 years. At 4 years of age, she developed migraine which was precipitated by exposure to bright sunlight, and excessive heat, and was aggravated by eating chocolate. She was put on an elimination diet which indicated that in addition to chocolate, egg also caused migraine.

CASE 10843.—A boy with migraine since the age of 4 years was also a behavior problem and did not get along well in his school work despite a superior I. Q. Chocolate was known to cause headache, and egg, milk, and apple were suspected. By elimination diets, it was discovered that he reacted with migraine or mental confusion to chocolate, wheat, pork, and a few other foods of less importance. When he keeps strictly to his diet, he does well and his appetite greatly improves.

CASE 10324.—This girl was perhaps the most dramatic case studied. She was first seen at the age of 10½ years because of migraine, which had started at the age of 8½ years. When first seen, she was having attacks almost daily which were becoming progressively severer. She had had asthma in early infancy and, since the age of 6 years, perennial allergic rhinitis. Her father suffered from asthma. On a strict elimination diet, she made a remarkable recovery. Egg and chocolate were eventually shown to be the foods most important in causing her difficulty.

SUMMARY AND CONCLUSIONS

Migraine occurs in children of all ages from infancy onward.

A past personal history of allergy or a family history of allergy may be suggestive but is not conclusive in the diagnosis of migraine of allergic origin in childhood when such a diagnosis is in doubt.

In some instances, childhood migraine may be of allergic origin and due to foods, commonest of which are chocolate, egg, wheat, and milk.

Skin tests are of no value, the offending foods most commonly being found, when not already known by experience, by means of elimination diets.

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

BREASTFEEDING IN CASES OF PUERPERAL MASTITIS. R. HOLLANDER, Deutsche med. Wchnschr. **78**:1770 (Dec. 18) 1953.

In 8,696 deliveries, 191 cases of mastitis occurred. In four of these cases, a purulent mastitis antedated birth. In 13, it occurred after delivery, with abscess formation. When no signs of abscess formation existed the infants were not taken off the breast, that is, in 188 cases. These infants did not show any injurious effect referable to the mastitis, with the exception of two cases where diarrhea and purulent skin eruptions might have been related to the mastitis. In cases where a disease of the infant might possibly be related to a mastitis, it is recommended that the breast be emptied and the milk given after boiling.

AMBERG, Rochester, Minn.

Vitamins; Avitaminoses

NATURE OF THE "VITAMIN A-LIKE FACTOR" IN LARD. S. F. HERB, R. W. RIEMENSCHNEIDER, HANS KAUNITZ, and CLARK A. SLANETZ, J. Nutrition **51**:393 (Nov. 10) 1953.

Biological assays have indicated that different samples of lard usually have a vitamin A activity equivalent to about 0.4 to 2 units per gram. It is concluded that typical vitamin A is present in lard and probably accounts for most of its biological vitamin A activity. The possibility of the presence in lard of other substances possessing similar activity but differing chemically from vitamin A is not completely excluded but is considered unlikely. The finding of vitamin A in lard also renders unlikely previously published assertions that lard has a so-called "sparing" action on added vitamin A when it is isocalorically substituted for other nutrients, such as carbohydrate and protein.

FREDEEN, Kansas City, Mo.

VITAMIN A AND BETA-CAROTENE IN MOTHERS' MILK UNDER SOME EXPERIMENTAL CONDITIONS. A. CALZETTI, Clin. pediat. **35**:520 (July) 1953.

The giving of vitamin A to nursing mothers increased the vitamin A but not the beta-carotene content of their breast milk. The feeding of 200 gm. of carrots daily resulted in an increase in both the vitamin A and the beta-carotene content of the mother's milk.

HIGGINS, Boston.

THE EFFECT OF VITAMIN E ON THE ELECTROPHORETIC BLOOD PROTEIN PICTURE. M. GOMIRATO-SANDRUCCI, Minerva pediat. **5**:903 (Oct. 31) 1953.

The giving of vitamin E to children resulted in no striking changes in the blood protein picture as tested by electrophoresis, except for an increase in the amount of fibrinogen; this increase was present two hours after the vitamin was taken, but was no longer found after four hours.

HIGGINS, Boston.

STUDY OF VITAMIN T (TORUTILIN). L. TORRES MARTY and J. VALE BANARES, Arch. pediat., Barcelona **4**:411 (Jan.-Feb.) 1953.

The authors describe the early work on insects (termites) done by Goetsch and his discovery and research on the biological catalyst which was named vitamin T by its discoverer.

They discuss its use clinically in a variety of cases. Its action reinforces the action of other vitamins, especially vitamin D. It helps in the synthesis of proteins and regulates the metabolism

of lipoids. It seems to have an effect on the endocrine system comparable to that of the hypophysis, especially in the stimulation of growth in children.

The authors give in some detail the use of this catalyst in nutritional conditions such as celiac disease, rickets, and fractures in which callus is slow in forming; they also describe its use in eczema and other dermatological conditions. It seems to have a natural antihistaminic action, and good results have been reported in allergic diseases.

There are contraindications, such as acute infections and cases where the protein intake is very limited. Children with intestinal parasites should not be given vitamin T until the parasites are eliminated.

The studies of its effect on blood cells, etc. and its stimulating effects on cellular metabolism are described.

In the torutilina extract, folic acid, the citrovorum factor, and vitamins A and B_{12} have also been isolated.

ALLEN, Santa Fe, N. M.

EFFECT OF SODIUM CITRATE-CITRIC ACID ADMINISTERED TO A CHILD WITH FLORID RICKETS. J. A. DE VRIES and T. H. J. HUISMAN, Maandschr. kindergeneesk. **21**:380 (Nov.) 1953.

The influence of a sodium citrate-citric acid mixture administered to a child of 9 months, suffering from florid rickets, is described. In contrast with reports found in the literature, no improvement was observed.

It is supposed that the amount of citric acid given was too high, and as a result the possibility of calcification in the bone was restricted. No influence of citric acid on the amino-aciduria was found. In this respect the effect of this drug differs from that of vitamin D.

FROM THE AUTHORS' SUMMARY.

Hygiene; Growth and Nutrition; Public Health

THE ECONOMIC ASPECTS OF NEW MILK LAWS. HANS BACHMANN, Bull. schweiz. Akad. med. Wissensch. **9**:325 (Dec.) 1953.

For the Swiss milk industry, the major economic problem arises from the relationship between the costs and prices of national and foreign milk products and from the legal prescription of prices covering a proper balance of production. Hence, the difficult task of obtaining a proper balance between cheese exports, butter production, and butter imports. The second economic problem is the quality pricing of milk. The more rapidly this is introduced the more difficult will be the utilization of the beef resulting from the extermination of infected animals, the raising of the necessary financial means, and the restoring of the level of the cattle population. As regards the organization envisaged in the Milk Statute, concern is expressed at the restriction of individual freedom, the total monopolization of the cheese export and the butter import, and the exaggerated concentration of power in the hands of a private body which is removed from public control on the one side, and which could, on the other side, under the law, shift the financial consequences of any major errors to the public.

FROM THE AUTHOR'S SUMMARY.

DATA AS TO THE MORE PREVALENT DISEASES SEEN IN THE PEDIATRIC CLINIC OF SIENA IN THE DECADE 1942-1951. L. LANDUCCI and M. L. CHITI, Lattante **24**:796 (Oct.) 1953.

The death rate among children admitted to the Pediatric Hospital in Siena in the war years (1942-1945) was 10.2%, while in the following six years, it was 4.3%. About 50% of the children admitted were under 2 years of age, and the ratio of boys to girls was 6:5. The percentages of the various disorders showed no consistent changes over the 10-year period. Of the admissions, 11.7% were for tuberculosis. The admissions or respiratory infections were more frequent in the winter months and for gastrointestinal and nutritional disorders in the summer months.

HIGGINS, Boston.

MORTALITY STATISTICS AMONG CHILDREN ADMITTED TO THE PEDIATRIC CLINIC IN MILAN IN THE DECADE 1944-1953. P. MENGHI, Minerva pediat. **5**:1043 (Nov. 30) 1953.

During the past 10 years, the fall in the death rates among children under 12 years of age treated in the clinic in Milan has been most marked in cases of tuberculous meningitis, purulent meningitis, prematurity, and respiratory infections. In 1953, the following conditions show the highest percentages of deaths among children admitted for treatment: blood dyscrasias (28%), prematurity (20%), chronic malnutrition (17%), neonatal disorders (13%), tuberculous meningitis (13%), infectious diseases (10%), purulent meningitis (8%), respiratory infections (5%), and acute nutritional disorders (4.8%).

HIGGINS, Boston.

THE EVALUATION OF SKELETAL DEVELOPMENT IN NORMAL AND PATHOLOGICALLY ABNORMAL CHILDREN AND ADOLESCENTS. G. COTELLESSA and E. DE TONI, Pediatria **61**:872 (Nov.) 1953.

Five hundred children have been evaluated as to how their body weight, height, and skeletal development compared with the accepted normal findings for their age. The determination of the skeletal age should afford a useful index of general body maturity.

HIGGINS, Boston.

BIOMETRIC STUDY OF SCHOOL CHILDREN OF MODENA. EMILIO REZZA and ERIO SORGANI, Riv. clin. pediat. **51**:721 (May) 1953.

In the first part, some criteria of auxological methodology are presented, with special reference to the conception of normality and to the auxological standards and their application. Some well-known methods for the contemporary study of two dimensions are also reported.

The second part contains the exposition and discussion of the results of a biometrical research made in consideration of the size, weight, and perimeter of the chest of Modena schoolboys from 6 to 12 years of age. From the relative data are drawn the standards for the three measures, taken separately.

The third part deals with the experiments made with such data on De Toni, Correnti, and Wetzel methods for the study of two measures, considered contemporarily. Advantages and disadvantages of each method are also discussed.

FROM THE AUTHORS' SUMMARY.

PROTECTION OF THE PHYSICALLY HANDICAPPED CHILD. CONRADO PELFORT, Rev. españ. pediat. **9**:505 (May-June) 1953.

The author is the president of the National Association for Handicapped Children in Uruguay. He analyzes the stages of development of the program in Uruguay for the physically handicapped child, including orthopedic defects, vision and auditory deficits, rheumatic fever, asthma, epilepsy, diabetes, etc.

The position and contributions of private and governmental agencies in the development and maintenance of the program is explained. The first necessity, the author believes, is a survey in which a register of each type of handicap is kept.

Day schools serve certain needs, and institutions like the one in Montevideo named for Franklin Delano Roosevelt serve other types of handicaps. Teachers, psychologists, etc. are necessary to keep the child alert and learning as well as happy, so that he may be able to take his place in society later.

ALLEN, Santa Fe, N. Mex.

BIOMETRIC STUDIES OF SPANISH INFANTS. E. JAS, S. RIOS, A. ARBELO, J. BEJA, and S. NAVARRO SAGUSTA, Rev. españ. pediat. **9**:1039 (Nov.-Dec.) 1953.

This is a biometric study of 1,600 healthy babies. All premature infants or those with low birth weight, as well as any with illness of a prolonged or unusual nature, were excluded. Each child was weighed and measured every week, beginning at 1 week and ending at 53 weeks.

The variables studied were weight, height, sitting height, cephalic perimeter, thoracic and abdominal perimeter, and size of the fontanel. Certain equations were evolved.

The authors believe that such studies should be made in other parts of Spain for any valid conclusions, as these children were all from middle-class economically comfortable families in Madrid.

ALLEN, Santa Fe, N. Mex.

INFANT MORTALITY IN CHILE. GUILLERMO ADRAISOLA, Rev. chilena pediat. **24**:483 (Dec.) 1953.

A study is made of infant mortality in Chile in its epidemiology and according to medical diagnosis.

The epidemiological study shows that infant mortality in Chile is high compared with other countries that register with the World Health Organization, although it shows a constant diminution in the last decades, diminution that has accelerated since 1936. It appears associated with conceptional and genetic factors, such as the sex of the child, the weight at birth, the age and parturition of the mother, and a combination of external influences difficult to separate, such as economic conditions, urban concentration, the percentage of birth and legitimacy, medical attention during birth, the seasons of the year, and the age and nutrition of the child.

The greater winter mortality and the relatively greater late mortality than neonatal suggest that the weight of adverse conditions of the weather are still very strong in Chile. Infectious diseases cause more than 50% of infant deaths. The bettering of sanitary standards is still in Chile the most important sanitary action leading to a lower infant mortality.

Analysis of the diseases that are registered as causing the greatest number of infant deaths shows that the nonprofessional certificate is still very high and that the medical certificate is not efficient. It is especially important that exact knowledge of the causes of infant deaths makes necessary the adoption of the norms of certification recommended by the International Commission (6th revision), whose advantages are now being shown.

FROM THE AUTHOR'S SUMMARY.

PRINCIPLES AND ILLUSTRATIONS OF GROUP THERAPY IN CHILDREN. J. FISCHER, Pediat. listy **8**:21, 1953.

At first, the author presents a theoretical account of the aims, mechanism, and technique of group therapy in children. These problems are illustrated in the case of four children in his first therapeutic group, and the role of the various factors which contributed to the therapeutic successes is evaluated. In conclusion, the author summarizes briefly the conditions which, in his opinion, should be observed in order to attain the best possible results in the group treatment of children.

FROM THE AUTHOR'S SUMMARY.

Prematurity and Congenital Deformities

MICROSCOPIC INVESTIGATIONS INTO THE CAPILLARIES OF NEWBORN, ESPECIALLY PREMATURE INFANTS. TERTTU ARAJÄRVI, Études néo-natal. **2**:139 (Sept.) 1953.

The blood vessels of the conjunctiva of 264 newborn infants and infants under one year of age were examined using a binocular capillary-microscope, magnifying 36 to 60 ×. Sixty-four of the infants were premature, weighing under 2,500 gm. at birth. The age of the infants varied from 15 minutes to 8 months; however, the majority, 231 infants, were under 14 days of age at the first examination. Photographs have been taken of the conjunctiva of 38 infants.

In order to test the reactivity of the conjunctival capillaries of the newborn to extrinsic stimuli, 2 to 3 drops of epinephrine hydrochloride solution, diluted 1 : 1,000,000 or 1 : 100,000, were instilled into the infant's eye. The conjunctival blood vessel network of the newborn, compared with that of the adult, was much more confused. Locally in the conjunctiva the newborn had plenty of both thicker and thinner vessels crisscrossed above one another; in other

places they were few. A feature common to the premature newborn was that the loops of the capillary network were pronouncedly larger and the distribution of the vessels seemed less regular still than with the full-term babies. However, individual differences were numerous.

During the first six to nine weeks, with a somewhat longer period for premature than for full-term babies, the capillaries developed considerably. They increased and became thinner and more regular. After this the development continued more slowly. The conjunctival blood vessel network of children of 6 to 8 months of age seemed completely similar to that of the adults.

With 48 full-term infants under 14 days old, with a birthweight of over 2,600 gm., the conjunctival capillaries reacted to epinephrine hydrochloride dilution 1 : 1,000,000 by contracting. With 19 premature infants, also under 14 days of age, weighing under 2,400 gm. at birth, the capillaries did not contract on stimulation with this dilution, whereas they did with a 10 times higher concentration, 1 : 100,000. Infants weighing over 2,600 gm. included 1, and those weighing under 2,400 gm., 10, whose blood vessel reaction differed from the above. In the weight group of under 2,600 but over 2,400 gm., there were 10 infants, and the capillary reactivity of this group showed the greatest variation; with an average of half of them, the capillaries contracted with an epinephrine dilution of 1 : 1,000,000. The reaction varied, often evidently due to the difference in time between the calculated and the real date of birth. The child's age also affected the reaction greatly. With premature infants, the conjunctival capillaries often began to contract at the age of one week with an epinephrine dilution of 1 : 1,000,000; though the contraction was partial and still slow, two weeks after birth their capillary reaction was fully similar to that of full-term babies.

No aggregation of red cells was observable in the conjunctival vessels of the healthy newborn and infants under one year old. One hundred sixteen newborn infants were studied under the capillary microscope immediately after birth before the silver nitrate instillations, which caused a local inflammation in the eyes and also a slight red cell aggregation. This persisted for one to two days. Intravascular red cell aggregation was observable in the conjunctival blood vessels of newborn infants (*a*) after abnormal deliveries; (*b*) after major hemorrhages during delivery; (*c*) in infants affected with hemolytic disease of the newborn; (*d*) with infants who had evidently been infected intrauterinely or during delivery.

Intravascular red cell aggregation was observable in the conjunctival vessels of infants over 2 days but under 1 year old (*a*) with infants suffering from hemolytic disease of the newborn, in which case the severity of red cell aggregation was proportionate to the other examination findings and symptoms. Where exchange transfusion was performed, the red cell aggregation diminished immediately and disappeared completely in four to five days; (*b*) in various infections, when the severity of red cell aggregation was again proportionate to the severity of the other symptoms of infection. A slight red cell aggregation was often the first symptom of an incipient infection. The severity of red cell aggregation seemed proportionate also to the severity of the anemia present during the infectious disease.

FROM THE AUTHOR'S SUMMARY.

AN ANALYSIS OF THE CAUSES AND FREQUENCY OF PREMATURITY, ESPECIALLY DURING THE WAR YEARS. M. VERROTTI, Lattante **24**:449 (July) 1953.

Some statistics as to prematurity, covering the years 1936 through 1950, are given as gathered from the records of the clinic in Siena, Italy. Of the 10,799 infants, 5.4% were born prematurely; in the prewar years the percentage was 3.5%, in the war years, 5.0%, in the early postwar years, 7.5%, while in 1950, the percentage had fallen to 5.2. Among the premature infants, 54% were boys and 46% girls; 36% were born before the eighth month of pregnancy, and 55% were born of primiparae. But the death rate due to prematurity had not increased during this period.

HIGGINS, Boston.

COMMENTS ON VARIOUS PROCEDURES FOLLOWED IN THE FEEDING OF PREMATURE INFANTS. E. DE TONI, Lattante **24**:458 (July) 1953.

In a discussion of the results of different routines and formulae used in the Premature Center of the University of Genoa Children's Hospital, the author comments that mother's milk, even if modified more or less, is the fundamental basis for securing a correct and safe diet and for obtaining a constant weight gain.

HIGGINS, Boston.

CLINICAL AND PATHOLOGICAL STUDY OF THE "STATUS BONNEVIE ULLRICH." E. PENNATI, Minerva pediat. **5**:936 (Oct. 31) 1953.

A 13-year-old girl born with multiple congenital malformations died from gastroesophageal hemorrhages. An autopsy revealed, in addition to cirrhosis of the liver, a greatly enlarged spleen, abnormalities of the pancreatic and salivary ducts, and diffuse cystic degeneration of the thyroid, the ovaries, and the liver. The author discusses the possible relation of these findings to the etiology of the Bonnevie-Ullrich syndrome.

HIGGINS, Boston.

PROGERIA. P. DURAND, Minerva pediat. **5**:1021 (Nov. 30) 1953.

A 12½-year-old boy with a mental age of 14 2/12 years had had marked jaundice at birth and has always been dwarfed. He had little subcutaneous fat, marked arteriosclerosis, reduced pituitary, adrenals, and testicular functions, and several bone abnormalities. His electroencephalogram was of the adult type. He appeared to have a typical case of progeria, which is presumably a generalized dysfunction of the endocrine glands.

HIGGINS, Boston.

GARGOYLISM. S. CORBO, Pediatria **61**:934 (Nov.) 1953.

A boy 3 years of age presented the typical picture of gargoylism (Hurler's syndrome), with dwarfism, dysosteogenesis, hepatosplenomegaly, deafness, and mental deficiency. There was no evidence of pathological aminoaciduria. This is the 6th case of Hurler's syndrome to be reported in the Italian literature in the past two years.

HIGGINS, Boston.

PERSISTENT URACHUS. INES ULLOA ACUNA, Rev. chilena pediat. **24**:137 (May) 1953.

Four cases of patent urachus, including their pathology, radiology, and clinical courses, are reported.

Two of them, girls, also presenting vesicoumbilical fistulae, were seen at one month of age and operated upon during the second month. Both recuperated without complications.

The other patients, one a little boy and other a little girl, presenting suppurated cysts of the urachus, were seen during their second year and 15 days after the onset of the disease. In both, the pus was evacuated, and, after treatment with antibiotics, the cysts were removed and very good results obtained.

A summary of the embryology, pathology, and histology of urachus is given as well.

FROM THE AUTHOR'S SUMMARY.

AGE OF MOTHER AND MALFORMATION OF THE OFFSPRING. HANS GREBE, Med. Klin. **48**:293 (March 6) 1953.

Some correlation of the age of the mother is accepted for Mongolism, chondrodysplastic dwarfism, and acrocephalosyndactylism. Oxygen deficiency is stressed in the genesis of malformations.

AMBERG, Rochester, Minn.

PRENATAL PATHOLOGY. O. THALHAMMER, Wien. klin. Wchnschr. **65**:1001 (Dec. 11) 1953.

This review is a discussion of the various factors which may lead to injuries of the fetus, such as its age and the kind of injurious agents, and stresses the importance of individual and familial influences. The injurious agents are enumerated and classified as poisons, infections, and deficiency states. These exogenous agents require also a disposing endogenous factor. Emphasis is laid on the importance of these factors in the production of fetal lesions as contrasted to those arising from genetic origin.

AMBERG, Rochester, Minn.

Acute Contagious Diseases

POLIOMYELITIS: IS IT A PROBLEM OF THE LARYNGOLOGIST? M. W. SIMMONS, Eye, Ear, Nose & Throat Month. **32**:383 (July) 1953.

The laryngologist in the poliomyelitis team is essential to the successful treatment of respiratory complications in acute poliomyelitis. He has been trained to recognize respiratory problems. Early recognition of respiratory distress will help materially to reduce the mortality of acute poliomyelitis. Tracheotomy is a lifesaving procedure to relieve respiratory obstruction caused by hypersecretions, by loss of the laryngeal sphincter action, with spillage of food, fluids, and vomitus into the airway, and by flaccid vocal cords. Respirator patients pose a problem because of the loss of the cough reflex and may require tracheotomy. Respiratory acidosis from accumulation of carbon dioxide and metabolic acidosis from oxygen-starved tissues produce a progressive symptom pattern leading to coma and death, unless there is prompt intervention to relieve the obstruction to breathing. The victim of poliomyelitis with restlessness and uncooperativeness may have interference with his airway and needs immediate treatment. Tracheotomy is a safe procedure, free from complications, must be performed early, and is much more effective than postural drainage and aspiration alone.

This article is based on the experience and observation of 281 patients with acute poliomyelitis admitted to the Fresno County General Hospital, Fresno, Calif., in the years 1950, 1951, and 1952. There was a total of 92 patients with bulbar and bulbospinal poliomyelitis. Tracheotomies were performed on 41 patients. During this period, there was a total of 18 deaths. In all patients undergoing postmortem examination, lung involvement was observed, consisting of pneumonia, atelectasis, and pulmonary edema. Hemorrhage in the brain was explained by the asphyxia and not by action of the virus. Often the tracheotomies, especially in the earlier years, were delayed because of late admissions, and lung complications had already supervened.

Familiarity with the symptoms associated with inadequate respiratory exchange may prevent many deaths. Early symptoms include headache, increased mental activity, agitation, sweating on the forehead, dyspnea, uncooperativeness, anxiety, and restlessness. Euphoria is also sometimes observed. Later, confusion, disorientation, and irrationality are observed, leading to convulsions, unresponsiveness, lethargy, and coma. When a patient is antagonistic toward everything done for him, with combativeness toward the attendants, one must immediately suspect interference with the respiration. Sedative drugs, especially opiates, are contraindicated, because the patient is struggling for all the air he can obtain. Increase in pulse rate and a very high blood pressure very frequently accompany this condition. Cyanosis is not a sign to be awaited to perform surgery. When it occurs, the prognosis is much more uncertain. Too many times symptoms are blamed on the encephalitis accompanying the disease. This difficulty arises because the symptoms are similar in respiratory obstruction and in encephalitis. Only when it is certain that the airway is clear can the symptoms be ascribed to encephalitis. Polioencephalitis occurs with each case, but one must consider the above-mentioned symptoms on a respiratory etiology in order to prevent deaths.

Anoxia is not the important cause of the symptoms. Decreasing the oxygen intake may produce unconsciousness without distress or premonition of danger. It is the increased carbon dioxide concentration which causes extreme distress, apprehension, and fear of impending death. Longer exposures and high concentrations of carbon dioxide cause anesthesia, respiratory depression, convulsions, narcosis, and circulatory collapse. In asphyxia, anoxia, compared to the respiratory acidosis, represents only a small part of the picture.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

STUDIES ON RUBELLA IMMUNIZATION. SAUL KRUGMAN, ROBERT WARD, KATHRYN G. JACOBS, and MARTIN LAZAR, J. A. M. A. **151**:285 (Jan. 24) 1953.

Rubella was transmitted to susceptible human volunteers from nasal washings during the first day of the rash even after the material had been kept at 70 C. for nine months. It was transmitted from the blood by intramuscular injections two days before the rash. The incubation period

was usually a little shorter, 9 to 16 days. Not infrequently the disease appeared with nodes and fever but no rash, yet the disease was transmitted with the typical three-day rash. The danger of creating such a widespread epidemic that it would include women in the first trimester of pregnancy was mentioned.

KIMBALL, Evanston, Ill.

CHLORAMPHENICOL IN PERTUSSIS. G. SINGH and J. S. NEKI, J. Indian M. A. **22**:146 (Jan.) 1953.

Of nine cases of pertussis treated with chloramphenicol, three recovered in one week, three recovered and had a relapse, and three apparently were improved but were not followed up. The author concludes that the drug shows promise and should be tried further.

McGUIGAN, Evanston, Ill.

INCIDENCE OF POLIOMYELITIS FOLLOWING TONSILLECTOMY OR ADENOTOMY. I. P. VALD POULSEN, Acta oto-laryng. **43**:482 (Aug.-Oct.) 1953.

Vald Poulsen investigated 750 cases of poliomyelitis in an epidemic in Denmark in 1950. These were investigated to see if there might be a causal relationship between recent tonsil and adenoid surgery and the incidence of poliomyelitis and also to determine if there might be a higher incidence of poliomyelitis of the bulbar type within the operated group. The stated investigation gave no statistical evidence in support of the theory that poliomyelitis, particularly that of the bulbar form, occurs any more frequently among patients who recently have undergone a throat operation.

ROBERT LEWY, Chicago [A. M. A. ARCH. OTOLARYNG.].

Acute Infectious Diseases

WESTERN EQUINE ENCEPHALITIS IN INFANTS. HENRY B. BRUYN and EDWIN H. LENNETTE, California Med. **79**:362 (Nov.) 1953.

Approximately one-third of the laboratory-confirmed cases of Western equine encephalitis occur in children under the age of 10. The present paper describes three instances of Western equine encephalomyelitis virus infection in infants under one year of age, together with the resultant sequelae. The difficulties associated with diagnosis of central nervous system disturbances in very young children are discussed, and it is pointed out that, in view of the frequent ocurrence of clinical infections with the arthropod-borne encephalitis viruses, these agents should be given serious consideration as a cause of acute central nervous system infection in childhood and as the possible etiology for obscure severe neurological disturbances in the pediatric age groups.

PRYOR, Redwood City, Calif.

TREATMENT OF INFECTIOUS MONONUCLEOSIS WITH CORTICOTROPIN. CHARLES E. BENDER and BENJAMIN C. HOUGHTEN, Northwest Med. **52**:922 (Nov.) 1953.

The authors present 11 cases to show that when infectious mononucleosis is of more than average severity, corticotropin is effective in reducing the pharyngeal inflammatory reaction, in particular, and in reducing the severity of the illness in general.

With 20 mg. of corticotropin given intermuscularly every six hours for two days, and thereafter reduced in stepwise fashion for an average duration of six days, there were no significant abnormalities, side-reactions, complications, or contraindications noted.

DOCTER, Seattle.

ROSEOLA INFANTUM. FE DEL MUNDO and LETICIA S. CORDERO, Philippine J. Pediat. **2**:6 (April-June) 1953.

Thirty cases of roseola infantum are presented in this paper to bring out the characteristic picture of the disease as observed among our Filipino patients. Each case followed a consistently characteristic pattern of high fever for two or three days, with fall by crisis, at which time a

macular or maculopapular rash was observed. This rash completely disappeared in about two days. The blood showed a moderate leukopenia. There were no characteristic physical findings. No complications were observed, and none of the cases ended fatally. The symptoms in our cases followed the same patterns as those described by authors abroad.

FROM THE AUTHORS' SUMMARY.

MYOPATHY AND SEQUELAE OF POLIOMYELITIS: VALUE OF THE MUSCLE ROENTGENOGRAMS. ANDRE GROSSIORD, JACQUES BERNARD, and RENE MARTEAU, Presse méd. Supp. 67, p. 1353 (Oct. 21) 1953.

After full description of a case in an 11-year-old boy, the authors point out that the coexistence in the same patient of a myopathy and poliomyelitic sequelae has been reported several times. They wonder whether this conjunction of two different diseases is merely casual and suggest that the "short-term-favoring" factors, such as peripheral traumas, should be considered more than the "long-term-favoring" factors, such as diverse malformations, neurologic or orthopedic affections, and familial fragility.

As regards particularly the myopathy, it was possible to affirm the pathologic association to be due to mere coincidence because of the difference observed between the deficits in the two lower limbs. Finally, the authors describe the roentgenological features of myopathy.

FROM THE AUTHORS' SUMMARY.

PERTUSSIS VACCINATION AND ITS CONTRAINDICATIONS. E. KONG, Helvet paediat. acta **8**:90 (March) 1953.

A survey of the world literature is given concerning cases of cerebral complication following pertussis vaccination. There is a description of two personal cases. From this study, it appears that one should not vaccinate children against pertussis under the following conditions: (1) family history of nervous disease, (2) history of convulsions in the child, (3) allergic diseases, (4) poor general conditions, and (5) evidence of acute infectious diseases.

Injections should not be continued if there is a severe reaction at the first or second injection.

For little children and babies in good health, pertussis vaccination gives a worthwhile protection against pertussis, which is often severe at these ages.

FROM THE AUTHOR'S SUMMARY.

PRIMARY HERPETIC INFECTION WITH HEPATITIS IN A BOY FOUR YEARS OF AGE. P. TOLENTINO and F. DE MATTEIS, Clin. pediat. **35**:461 (July) 1953.

A liver biopsy was taken in the case of a 4-year-old boy with acute aphthous stomatitis, cervical adenitis, hepatomegaly, splenomegaly, and meningismus. The liver tissue was found to be infiltrated by mononuclear cells; the parenchymal cells showed inclusion bodies and degenerative changes. This finding must indicate a widespread diffusion of the virus of herpes simplex by means of the bloodstream.

HIGGINS, Boston.

TWO CASES OF POLIOMYELITIS APPEARING AFTER APPENDECTOMY. D. GOTTI, Clin. pediat. **35**:466 (July) 1953.

Of 3,500 cases of poliomyelitis observed at the Pediatric Clinic in Bologna, only two could be correlated with appendicitis and appendectomy. In each of these cases, the paralysis became apparent on the third day after the operation. One of the children had had an influenzal infection one week before the operation. It would appear that the operative trauma may have led to a spread of the virus from the intestine to the nervous system.

HIGGINS, Boston.

THE URINARY FINDINGS IN THE ACUTE PHASE OF POLIOMYELITIS. B. RONDININI and M. MALOSSI, Clin. pediat. **35**:845 (Nov.) 1953.

Of 535 patients examined in the acute phase of poliomyelitis during epidemics in 1950, 1951, and 1952, only 6 had red blood cells in their urine specimens, and 31 had white cells and epi-

thelial cells. In 1953, 271 patients were similarly examined; 21 had red cells and 48, white and epithelial cells in the urinary specimens. It may be that these urinary findings indicate a localization of the virus in the kidney; this should be the basis for more careful study in future epidemics.

HIGGINS, Boston.

THE EFFECT OF CORTICOTROPIN (ACTH) ON ANTIBODIES AND ON THE INDICES OF IMMUNITY. E. SEGAGNI, E. ARDITI, and C. ALUFFI, Minerva pediat. **5**:180 (March 31) 1953.

Tests with rabbits showed that the giving of corticotropin (ACTH) lessened the effect of the giving of typhoid vaccine to produce a very positive Widal reaction. The giving of corticotropin caused a definite change in the opsonins of human blood; but these changes were not consistent, being sometimes up and sometimes down.

HIGGINS, Boston.

PNEUMONOPATHY FROM ORNITHOSIS IN CHILDREN. F. TOSCANO, G. C. ANGELA, and F. DI NOLA, Minerva pediat. **5**:930 (Oct. 31) 1953.

An 18-month-old boy contracted a severe pneumonitis, lasting two months, migratory in type, and accompanied by some pleurisy. The patient lived on a poultry farm; two hens had recently been found dead, having had diffuse intestinal and ovarian hemorrhages. Compliment deviation tests were found positive, with a virus of the psittacosis group.

HIGGINS, Boston.

CLINICAL STATISTICS OF MALIGNANT DIPHTHERIA IN THE PEDIATRIC CLINIC IN FLORENCE IN THE YEARS 1933-1951. PIERO MOGGI, Riv. clin. pediat. **51**:77 (Aug.) 1953.

After giving the statistical data on cases of malignant diphtheria in patients of the Pediatric Clinic of Florence from 1933 to 1951, the author reviews the pathogenic theories of the disease, dealing more particularly with the most recent theories and emphasizing the importance of the presence of a diffusing factor in the disease.

FROM THE AUTHOR'S SUMMARY.

TWO CASES OF EMBRYOPATHY DUE TO RUBELLA. E. MIRALBELL-ANDREU, Rev. españ. pediat. **9**:135 (Jan.-Feb.) 1953.

Two cases of cataracts are presented. One was unilateral and the other child had bilateral cataracts and congenital cardiopathy. Both mothers had suffered from rubella.

The child with one defective eye was born to a mother who had rubella during the first month of pregnancy and before she had missed her first menstrual period. The other mother suffered from rubella in the sixth week of pregnancy. This child also had the congenital heart lesion.

Discussion regarding prophylaxis includes the suggestion that 250 mg. of gamma globulin be given when any woman has been exposed to this infection.

ALLEN, Santa Fe, N. M.

ISOLATION AND STUDY OF VIRUS COXSACKIE IN CHILDREN WITH POLIOMYELITIS. ADALBERTO STEEGER, GUILLERMO CONTRERAS, and CELSO SANTIBAÑEZ, Rev. chilena pediat. **24**:271 (Aug.) 1953.

Four viruses from the feces of four infants have been isolated during the acute period of typical clinical poliomyelitis. The isolated viruses have the characteristics of the viruses in the Coxsackie group. For three of these isolated viruses there has been established through fixation of complement and neutralization an antigenic relation to three types of Coxsackie virus. The remaining virus presents all the characteristics of virus C but has not reacted with any of the 12 prototypes already investigated.

In the serum of one patient the appearance of neutralizing antibodies for the virus proper and for the respective Coxsackie prototype could be demonstrated during the course of the illness. In another patient the presence of these antibodies for the virus proper and the respective

Coxsackie was demonstrated in the only sample of blood available. The finding of these viruses, their characteristics and relationships with the Coxsackie group, and their possible pathogenic role are discussed.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF WHOOPING COUGH WITH ERYTHROMYCIN. CARLOS BAZAN M., GERMAN BATISTTINI M., and GERMAN PATIÑO MARTINEZ, Rev. chilena pediat. **24**:280 (Aug.) 1953.

From the results in 20 pertussis patients from 3½ months to 10 years of age treated with erythromycin, the following conclusions have been reached:

The bacteriostatic in vitro action of the erythromycin on Hemophilus pertussis Phase I is manifest. This action is noted from exposure to a concentration varying between 0.1 and 0.5 γ per cubic centimeter at 35 C. in 48 hours. Good results have been obtained by oral administration, using a dose of 30 to 50 mg. per kilogram of weight in 24 hours.

The average time of uninterrupted treatment for the clinical and hematological cure is estimated as 14.6 days. Relapse of symptoms is present in 20% of the cases.

The drug is a useful one, and its usefulness is indisputably demonstrated in 25% of the cases. In 95% of the cases there is no intolerance to the drug. It does not prevent bronchopulmonary complications; and when these are present, it has no effect in 80% of cases.

The author recommends further clinical investigation to improve the present results of treatment.

FROM THE AUTHORS' SUMMARY.

COMPARATIVE STUDY OF EFFICACY OF HETRAZAN, SANTONIN, AND HEXYLRESORCINOL IN THE TREATMENT OF ASCARIASIS. ENRIQUE FANTA NUNEZ, Rev. chilena pediat. **24**:284 (Aug.) 1953.

One hundred thirty-six children with ascariasis were treated with Hetrazan, santonin, and hexylresorcinol. With the doses used, 51.35% of partial successes and 27.02% of complete successes were obtained with Hetrazan; 59.45% and 24.32% with santonin, and 32% and 52% with hexylresorcinol. Hetrazan may be a useful drug in cases in which the classic medication cannot be used. Incidences of 46.7% and 77.21% of toxic manifestations with Hetrazan were observed. Among the toxic manifestations seen the author mentions four cases of pseudoacute abdomen that was erroneously diagnosed. The toxic manifestations in the series can probably be attributed to the high dosage given.

FROM THE AUTHOR'S SUMMARY.

STUDIES OF CHICKEN POX VIRUS. SEIJI ARAKAWA, ISAMU KONDO, TOMIO SEKI, and TIAKI KANEKO, Wien klin. Wchnschr. **65**:574 (July 10) 1953.

Serum obtained within 24 hours after the onset of fever from patients with chicken pox was injected into the brains of mice. The definite diagnosis evidently has to be made later. A monkey inoculated with the virus fixed in the mouse brain was taken ill with an eruption similar to human chicken pox. The virus can be grown on the chorioallantois membrane of the chick embryo. The serum of a patient from which virus had been isolated developed, in the course of days, an increasing neutralizing power against the fixed virus. The serum of rabbits immunized with the fixed virus acquired therapeutic and prophylactic activity. Electron microscopic measurements gave a size of 150 to 240 mg., while by ultrafiltration an average size of about 100 mg. was found.

AMBERG, Rochester, Minn.

Newborn

SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN INFANT. ROBERT E. IVY and FRED H. HOWARD, J. Pediat. **42**:600 (May) 1953.

A case of a newborn infant with extensive subcutaneous fat necrosis is presented. There was no evidence of trauma, infection, or asphyxia. There was no evidence of adrenal dysfunction. The cause and nature of this disorder remain obscure.

MACDONALD, Pittsburgh.

THE RADIOGRAPHIC APPEARANCE OF HYALINE DISEASE OF THE LUNGS IN THE NEWBORN. I. MESCHAN, VIDA H. GORDON, H. N. MARVIN, and G. REGNIER, Radiology **60**:383, 1953.

The histologic findings of the lungs of an infant who lived 32 hours explains the x-ray appearance in two chest roentgenograms. The roentgen findings were those of spotty soft tissue shadows in the right upper lobe, with radiolucency elsewhere. The sections of the tissue made later revealed that only 5% were aerated, the rest atelectatic. Markedly dilated bronchioles and alveolar ducts accounted for the expanded lungs seen on the roentgenograms. A hyaline membrane was seen in the aerated spaces of the bronchioles and alveolar ducts which the author believes prevented adequate interchange of gases and accounted for death.

ANSPACH, Riverside, Ill.

CORTISONE IN THE TREATMENT OF SCLEREMA NEONATORUM. REMEDIOS GOQUIOLAY ARELLANO and ROLANDO S. SONGCO, Philippine J. Pediat. **2**:10 (April-June) 1953.

The results obtained in the treatment of sclerema neonatorum with cortisone in seven infants are presented. Five of the infants recovered. Although this series is small, the dramatic results obtained justify the use of cortisone in the treatment of sclerema neonatorum, even though the exact mechanism of the action of cortisone on this disease is not known, because before the use of this hormone the disease had a very poor, if not almost fatal, prognosis.

FROM THE AUTHORS' SUMMARY.

THE RELATION BETWEEN MATERNAL AND FETAL PYRUVICEMIA AT BIRTH. G. CAFFARENA and M. MERLINI, Lattante **24**:517 (Aug.) 1953.

Analyses of the blood of newborn infants and of their respective mothers revealed that, in each case, there was more pyruvic acid in the blood of the mother than in the blood of the child. The author feels that hyperpyruvicemia of the newborn is probably not due to abnormal fat or carbohydrate metabolism of the baby, but merely due to passage of pyruvic acid from the blood of the mother when in labor to the blood of the child.

HIGGINS, Boston.

MALIGNANT TUMORS IN NEWBORN INFANTS: TWO CASES. PIERO E. CARRAI, Riv. clin. pediat. **51**:115 (Aug.) 1953.

The author refers to two cases of malignant tumors observed at birth and examines the opportunity of surgical treatment combined with roentgen and radium therapy as early as possible.

FROM THE AUTHOR'S SUMMARY.

PHYSIOLOGIC ICTERUS IN THE MATURE NEWBORN INFANT AND THE PREMATURE. F. RAGAZZINI, Riv. clin. pediat. **51**:188 (Sept.) 1953.

After a review of present etiological and pathogenetical theories of physiological icterus, the author did a statistical differential study in 444 newborn infants and 15 twins in order to point out the types of development of icterus in immature and in newborn infants at term, with special reference to the relationship between the degree of loss of weight and the rise and intensity of the icteric manifestation.

On the basis of the data obtained, it was possible to affirm that physiological icterus is much more frequent and intense in immature infants (95.98%) than in newborn infants at term (60%); moreover, the duration and intensity of the icterus is proportional to the degree of physiological loss of weight.

FROM THE AUTHOR'S SUMMARY.

BIRTH AND THE GENERAL SYNDROME OF ADAPTATION. JUAN J. MURTOGH and CARLOS MARTINEZ CASTRO, Rev. españ. pediat. **9**:237, 1953.

This study is subtitled "Some Considerations on the Blood Chemistry in the Newborn."

The chemical composition of the blood of newborn children was studied during the first 10 days to determine whether the biochemistry has any relation to the various phases of the general syndrome of adaptation.

Studies showed that during the first day of life the symptoms of shock from the chemical and humoral standpoint were present, but the equilibrium was beginning to be reestablished by the end of the first 24 hours. Sodium and glucose were low and ketone bodies high at birth. Chlorides, potassium, and CO_2 showed the changes typical of the adaptation found in countershock in the older child.

These studies were continued for 10 days and the conclusion from the studies (491 in all) is that from the blood chemistry findings, at least, the neonatal period ends after the fifth day of life.

ALLEN, Santa Fe, N. M.

RH DETERMINATIONS IN HUMAN INFANTS USING ANIMAL TESTING SERUM. INGEBORG FEHRMANN, Monatsschr. Kinderh. **101**:486 (Nov.) 1953.

Twenty-nine Rh-negative infants, as determined by human anti-Rh serum, were tested with anti-Rh serum obtained from guinea pigs. On the eighth day of life, 25 infants, and at 8 weeks of age, 20 infants had false positive reactions. At 6 months of age, they had all become negative. It was assumed that animal anti-Rh serum can be used for human Rh testing only after the first year of life.

HARTENSTEIN, Syracuse, N. Y.

THE DEVELOPMENT OF CHILDREN AFFECTED BY BIRTH TRAUMA. K. BRACHFELD, J. BRACHFELDOVA, J. SVATY, and H. TROJANOVA, Pediat. listy **8**:266, 1953.

The authors report concerning 69 children who were treated at the Second Children's Clinic, between Jan. 1, 1946, and Dec. 31, 1951, for acute severe conditions following birth injury and then followed up further at regular intervals. The prognosis of these children is uncertain and may be surprising by the quite favorable course they sometimes take, as well as by the very serious disabilities resulting at other times. Of all 69 children, followed over a longer period, 18 showed lasting aftereffects, 11 were severely affected, 7 were affected less seriously. The large number of microcephalics in the group shows that, in the development of microcephaly, this etiological possibility must be borne in mind. Nearly three-fourths of the children (74%) are still developing successfully and another seven (10%) will become, despite minor damage, proper members of the community.

FROM THE AUTHORS' SUMMARY.

Chronic Infectious Diseases

TUBERCULOUS MENINGITIS. M. P. BHAGAT, Indian J. Child Health **2**:18 (Jan.) 1953.

Tuberculous meningitis caused 11% of the medical admissions to a Bombay children's hospital in 1951. Eighty-eight cases admitted that year are analyzed.

Age incidence ran from 2 months of age to 8 years, with 60 cases between 6 months and 2 years. Fever was the commonest symptom, with personality changes the next most frequent sign. Lassitude, drowsiness, and anorexia occurred first in 23 cases, vomiting, in 35, convulsions, in 29, and paralysis, in 14.

Seventy patients died. None of these showed any response to therapy. Five cases were discharged as improved after stays of four to eight months. In none of these had the spinal fluid returned to an absolute normal.

MCGUIGAN, Evanston, Ill.

ISONIAZID IN EXTRAPULMONARY TUBERCULOSIS. P. N. TANEJA, Indian J. Child Health **2**:144 (April) 1953.

Isoniazid and isoniazid with streptomycin were used in 48 cases of extrapulmonary tuberculosis.

In primary tuberculosis, postprimary infiltration, and hilar adenopathy there was good response with both methods, with no advantage from the use of streptomycin. Similar results

were obtained in plural effusion, abdominal tuberculosis, tuberculous pericarditis, and tuberculosis of the bones and joints.

In meningeal tuberculosis, results indicated that isoniazid alone has no place in therapy and should always be combined with streptomycin.

The author feels that isoniazid is the treatment of choice in extrapulmonary tuberculosis other than meningeal.

McGuigan, Evanston, Ill.

Comparative Resistance of the Tubercle Bacillus to Streptomycin, Isoniazid, and a Streptomycin-Isoniazid Mixture. C. Choremis, S. Pantazis, and S. Stroumbou, Helvet. paediat. acta **8**:561 (Dec.) 1953.

Isoniazid is more effective against the tubercle bacilli in vitro than streptomycin. Streptomycin-resistant strains are not resistant to isoniazid. There are resistant strains which never had any contact with the drug. Strains resistant to both isoniazid and streptomycin are very sensitive to their combined use. The combination of streptomycin and isoniazid has a potentially synergistic effect on the tubercle bacilli.

From the Authors' Summary.

Preceding Pleurisy and the Degree of Reactivity to Tuberculin in Cases of Pulmonary Tuberculosis in Children. O. Zampori, Clin. pediat. **35**:147 (March) 1953.

One hunderd thirty out of 982 children with pulmonary tuberculosis in a sanatorium in Borno, Italy, had previously had symptoms of pleurisy. The clinical prognosis was regarded as unfavorable in 17% of these 130 children and in only 7% of the remaining 852 children.

Higgins, Boston.

The Endoarachnoid Treatment of Spinal Block in Tuberculous Meningitis by Isoniazid. M. Orlandelli and A. Degli Esposti, Clin. pediat. **35**:162 (March) 1953.

Eight children, while under treatment for tuberculous meningitis with streptomycin intramuscularly and intrathecally and with the isoniazid orally, had developed a spinal block, with high spinal fluid protein and a paraplegia. The block was overcome, the spinal fluid protein lessened in amount, and the paraplegia relieved by the intrathecal administration of isoniazid.

Higgins, Boston.

A Comparison Between the Results Obtained by the Intradermal and the "Patch" Tests for Tuberculosis at a Children's Sanatorium. F. Margstahler, Gior. mal. infett. e parassit. **5**:176 (May) 1953.

Tuberculin tests were done on 652 children by both the Mantoux and the "patch" methods at a sanatorium. Fifty-one children had negative tests by both the Mantoux and the patch tests, 1 child gave a positive reaction only to the patch test, 24 children gave a positive reaction only to the Mantoux test, 576 children gave positive reactions to both tests. It was noted that the positive reaction could be detected earlier when the Mantoux test was used. The author lists the various techniques which have been described for making tuberculin tests and divides them into groups.

Higgins, Boston.

The Use of Amino Acids, Cytotoxic Serum, and Vitamin B_{12} for Dystrophic Infants Born of Tuberculous Mothers. A. Mallardi, Lattante, **24**:307 (May) 1953.

Ten dystrophic infants, born of mothers with tuberculosis, were treated at different times with (1) a protein dialysate by mouth, (2) vitamin B_{12}, and (3) the Bogomoletz cytotoxic serum injections (*Clin. pediat.* **34**:1 [Jan.] 1952). All three of the medications proved efficacious with these children.

Higgins, Boston.

ACTION OF CORTISONE IN EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS THAT ARE STREPTOMYCIN-RESISTANT. ROANO ROSSI and MICHELLE PARADISO, Riv. clin. pediat. **51**:100 (Aug.) 1953.

The authors have made experimental researches on guinea pigs respecting the action of cortisone on tuberculosis from streptomycin-resistant germs and found that the evolution of the disease appeared to be aggravated by the treatment.

FROM THE AUTHORS' SUMMARY.

TUBERCULOUS MENINGITIS AND PREGNANCY. A. MASI and P. MOGGI, Riv. clin. pediat. **51**:251 (Oct.) 1953.

After having gone through the medical literature of the subject, the authors refer to the clinicostatistical data drawn from the observation of 99 women aged more than 20 who had been admitted to the Pediatric Clinic of Florence for tuberculous meningitis.

In 23 of these women, the meningeal affection was more or less directly related with the pregnancy. A study had been made on these patients with special regard to the influence exerted by pregnancy on tuberculous meningitis and on the evolution prognosis and therapy of the disease. Such observations were compared with those made on the 76 women in whom tuberculous meningitis did not prove to be related at all with the state of pregnancy.

An attempt has been made to place meningitis chronologically in the general picture of the tuberculous disease.

In the second part of this study, the problem of congenital tuberculosis has been considered; two cases have been presented. Present pathogenetic views have been discussed at length. Lastly, the destiny of children born of women affected with tuberculous meningitis has been studied.

FROM THE AUTHORS' SUMMARY.

DIAGNOSTIC AND PROGNOSTIC EVALUATION OF LIQUOR SUGAR IN TUBERCULOUS MENINGITIS OF CHILDREN. MARIANNE GROLL-KAHL, Deutsche med. Wchnschr. **78**:407 (March 20) 1953.

The sugar content of the spinal fluid of 132 children with tuberculous meningitis was determined. At the first examination, normal values were found in about one-third of these patients, in the others, the values were diminished more or less. The patients were treated with streptomycin. Constantly diminished values or constantly diminishing values are prognostically unfavorable, but constantly normal values do not necessarily indicate a good prognosis.

AMBERG, Rochester, Minn.

BRONCHIAL CHANGES IN CHILDREN WITH PRIMARY TUBERCULOSIS OF THE LUNGS. E. CARLENS and H. HELLSTROM, Acta Pædiat. **42**:43 (Jan.) 1953.

The authors examined, bronchoscopically, 23 cases of primary tuberculosis of the lungs in children with clinical or radiographic signs of bronchostenosis. Bronchial changes were observed in 18 cases. In 13 of these cases, the changes were intrabronchial and were associated with caseous necrosis and tuberculous granulations. The diagnostic and therapeutic role of bronchoscopy is emphasized.

FROM THE AUTHORS' SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

MILD HEMOPHILIA: AN ALLELIC FORM OF THE DISEASE. JOHN B. GRAHAM, WILLIAM W. MCLENDON, and K. M. BRINKHOUS, Am. J. M. Sc. **225**:46 (Jan.) 1953.

A detailed hematological study of a large family with a mild form of hemophilia was made. This mild hemorrhagic disease is inherited as a sex-linked recessive characteristic and is manifested by easy bruising and prolonged bleeding after minor surgery. Diagnosis was made by the demonstration of a reduction in plasma antihemophilic factor to 15 to 20% of normal, while all other tests of blood-clotting function were normal. Since the assay of antihemophilic factor is relatively easy, the authors feel that a survey of unclassified persons with a bleeding tendency may be indicated to determine if these may be mild hemophiliacs.

SUTTON, Evanston, Ill.

PAROXYSMAL TACHYCARDIA IN EARLY INFANCY: TREATMENT WITH LARGE DOSES OF QUINIDINE. ARTHUR J. MOSS and ROBERT H. THOMPSON, California Med. **79**:51 (July) 1953.

A case of supraventricular paroxysmal tachycardia with 61 recurrences in a young infant is presented. Treatment with optimal doses of digitalis was ineffective, and ultimately the patient was maintained without paroxysm for more than 12 months before the condition finally abated.

The treatment of this condition, with emphasis on the use of quinidine, is discussed.

PRYOR, Redwood City, Calif.

SUCCESSFUL TREATMENT OF C. DIPHTHERIAE ACUTE BACTERIAL ENDOCARDITIS WITH CHLORAMPHENICOL, PENICILLIN, AND STREPTOMYCIN. G. E. DEANE and R. M. HIDEY, J. Pediat. **41**:473 (Oct.) 1952.

Penicillin, chloramphenicol, and streptomycin were combined in the successful treatment of acute bacterial endocarditis due to Corynebacterium diphtheriae.

MACDONALD, Pittsburgh.

ACUTE (INFANTILE) GAUCHER'S DISEASE. A. K. GEDDES and S. MOORE, J. Pediat. **43**:61 (July) 1953.

Gaucher's disease in infancy, in contrast to the disease in later childhood and adult life, is distinguished by disorders involving lack of pigment, striking tendency to neurological symptoms, an acute malignant course, and early death. Geddes and Moore describe a case of a 3½-month-old infant, complete with necropsy findings. Chemical analysis of the spleen and liver showed the glucosidocerebroside characteristic of this disease.

MACDONALD, Pittsburgh.

COARCTATION OF THE AORTA. W. B. HUTCHINSON, Northwest Med. **52**:932 (Nov.) 1953.

Three cases of coarctation of the aorta with successful surgical correction are presented. The clinical features, diagnostic criteria, and anatomic and pathological findings at operation are discussed. The importance of early diagnosis and the ideal age for surgery are stressed.

DOCTER, Seattle.

MUCOLYTIC ENZYME SYSTEMS: XX. COMPARISON OF MUCOPROTEIN AND HYALURONIDASE INHIBITOR IN MATERNAL AND INFANT SERUM. ROBERT A. GOOD, VINCENT C. KELLEY, THOMAS A. GOOD, and DAVID GLICK, Pediatrics **12**:575 (Nov.) 1953.

Normal maternal serum and newborn infant serum have been compared with respect to their content of nonspecific hyaluronidase inhibitor and mucoprotein. Elevations in serum levels of hyaluronidase inhibitor and mucoprotein were found in maternal serum, while decreased concentrations of mucoprotein and normal levels of hyaluronidase inhibitor characterized the serum of infants at birth. Mucoprotein concentrations in maternal serum increase for a period following delivery and remain at high levels for at least one month. Increase from low mucoprotein levels occurred in infants' serums during the first month of life, and levels comparable to those of normal adults were found throughout the remainder of the first year. The relation of these findings to studies of other protein constituents in maternal and infant serum is discussed, as are possible mechanisms to explain the results obtained.

FROM THE AUTHORS' SUMMARY.

ATYPICAL LEUKEMIA. EUGENE STRANSKY and AMBROSIO REYES, Philippine J. Pediat. **2**:15 (April-June) 1953.

There are cases of leukemia in which the typical hematologic findings may be absent either in the blood alone or even in both blood and bone marrow. In such cases the leukemia is labeled atypical. Several case reports are presented and discussed. Atypical leukemia may develop spontaneously or may be the result of the new treatment with cortisone or corticotropin (ACTH). In the case of atypical leukemia, no diagnosis is possible without careful examinations of the bone marrow or of an aspiration specimen of the spleen.

FROM THE AUTHORS' SUMMARY.

HEMOLYTIC ANEMIA OF THE PREMATURE, WITH SPONTANEOUS FORMATION OF INTERNAL BODIES. C. GASSER, Helvet. paediat. acta **8**:481 (Dec.) 1953.

Severe spontaneous formation of Heinz bodies in the premature baby can produce serious hemolytic anemia. This has been described in 14 cases observed by the author. The main features are exclusive occurrence in premature infants or underweight full-term babies, icterus gravis, occurring generally after the first day and often prolonged, progressive anemia in the second to third weeks, usually coinciding with the decline of the jaundice, lack of splenomegaly, poor general condition, refusal of food, drowsiness, and vita minima.

In the blood, before the onset of anemia, there is a progressive formation of Heinz bodies in the first and second weeks; at the peak of the formation of Heinz bodies, there is a relative reticulocytopenia, usually followed by reticulocytosis, and very occasionally, hemolytic disease. Blood transfusion is the best therapy.

The etiology remains unclear. There is a lack of specific immune antibodies in the mother and child. There is no evidence of an exogenous toxic substance before, during, or after birth. The anemia is attributed to an adaptation difficulty of the premature. Pathogenesis may include splenic dysfunction, or an upset in the hemoglobin catabolism or in the protection mechanism of the red cells.

FROM THE AUTHOR'S SUMMARY.

CORTISONE AND CORTICOTROPIN IN THROMBOCYTOPENIA OF CHILDHOOD. VON C. GASSER and R. ANDERES, Schweiz. med. Wchnschr. **83**:1036 (Oct. 24) 1953.

The result of cortisone and corticotropin (ACTH) treatment in 10 cases of acute thrombocytopenia was compared with that in 10 cases observed prior to this treatment. In the untreated group were patients from 4 months to 14 years of age. In the treated group the age varied from 3 to 10 years. In the treated children, with one exception, a rapid, often rather excessive, increase in the number of platelets was registered.

In some patients not treated with cortisone, the platelets were restored to normal number—probably spontaneously. In others their number remained subnormal for long periods.

As compared with this group, the results of cortisone and corticotropin medication were striking, not only with reference to the increase in the platelets, but also with reference to the immediate improvement of capillary function.

AMBERG, Rochester, Minn.

ACTION OF VITAMIN E ON ACUTE MYOCARDITIS IN THE CHILD. AL LEONE and E. SULIS, Ann. ital. pediat. **6**:1 (Feb.) 1953.

The authors after a review of the action of various vitamins on the cardiac muscle and on the possible damage to the myocardium due to avitaminosic, dysvitaminosic, and hypervitaminosic conditions, report on their observations as to the action of vitamin E in cases of acute myocardial damage.

On the basis of their experience, they conclude that the tocopherolic treatment, although it does not have the same action as digitalis, is very useful in conditions of functional insufficiency because of an improvement of nutrition.

They recommend the introduction of vitamin E in those acute infections in which it is possible to note symptoms of cardiac damage.

FROM THE AUTHORS' SUMMARY.

FAMILIAL CONSTITUTIONAL FACTORS IN INDIRECT SEDIMENTATION RATES IN WELL AND SICK CHILDREN. G. MACCIOTTA, Ann. ital. pediat. **6**:85 (April) 1953.

The author examined the behavior of the rapidity of sedimentation in a large group of healthy and sick children and in their parents in order to draw from this some opinion on constitutional elements which may influence the phenomenon both in its physiological and its pathological expressions.

In his observations on healthy subjects, he found that generally the highest and lowest values in children corresponded to the same values in one or both parents; average values corresponded to average values in both parents or to a combination of high and low values in parents.

Although less evident, such correspondence was found in the group of pathologic children (bronchopneumonias, pneumonias, gastroenteritis, toxicoses, tubercular meningitis, nephropathies, typhus, and acute rheumatism).

The author thinks that the regularity of the rapidity of sedimentation is not entirely free athies, typhus, and acute rheumatism).

FROM THE AUTHOR'S SUMMARY.

BLOOD STUDIES ON PEOPLE LIVING IN WESTERN SICILY. F. LO JACONO and L. CONSAGRA, Clin. pediat. **35**:397 (June) 1953.

In view of the facts that Cooley's anemia is not frequently found in children in Western Sicily and is now recognized as of hereditary origin, the authors made blood studies on 100 healthy adults, a cross-section of the population of that region, to ascertain what deviations from the normal there might be in the red blood cells.

Thirty-seven of the subjects showed some abnormality in their red blood cells; 21 had increased fragility, 3 high red cell counts, 8 low hematocrit readings, 16 abnormally small red cells, and 6 low hemoglobin content. The increased fragility and the microcytosis were not consistently found in the same subjects.

HIGGINS, Boston.

Diseases of Nose, Throat, and Ear

A MODERN THERAPEUTIC REGIMEN FOR OTITIS EXTERNA. J. W. MCLAURIN, Eye, Ear, Nose & Throat Month. **32**:319 (June) 1953.

Each patient with otitis externa must be treated on an individual basis with the application of certain general principles. The patient must be given relief of pain or discomfort by analgesics or preferably by the use of small doses of x-ray. Cleansing of the external auditory canal must be done thoroughly and preferably manually by tip suction and cotton wipes. After suction is completed, cotton wipes dipped in alcohol are used. If the ear is too swollen and tender to permit cleansing by suction, it may be irrigated. The canal must, however, be left dry. If it is so tender that it cannot be wiped dry, it is irrigated with 95% alcohol and dried by compressed air. If the ear is too swollen and edematous to permit cleansing by irrigation, wicks saturated with Burrow's solution are utilized. At the end of 24 hours the edema and swelling are usually so decreased that the ear can be cleansed and the indicated therapy instituted at once. The causative agent should then be eliminated by the proper medication, after which the administration of such medication should be promptly stopped and general hygienic measures instituted to bring the external auditory canal back to normal.

Promiscuous application of the chemotherapeutic and antibiotic agents now available will not solve the problems of otitis externa. Unless these agents are applied according to definite principles, they are not only useless but also capable of doing considerable harm. Only those specific agents should be used to which the micro-organism present is known to be sensitive. The experienced otologist, on the other hand, can usually tell from his clinical examination whether the infection is caused by fungi or bacteria and if it is bacterial in origin, whether the causative micro-organism is Gram-negative or Gram-positive. Cultures are otherwise essential. The exudate for the culture must be taken under direct vision, and the culture medium should be streaked immediately. If Staphylococcus is the predominant organism, a coagulase test is run, and only if this test is positive, is the organism considered pathognomonic.

The therapeutic agent used must be employed in sufficiently high concentration to be immediately effective and should have a pH on the acid side. It must be applied in sufficient quantity to cover the entire surface, and it must be applied for a sufficient period at each application. McLaurin prefers to use an aqueous solution, as he feels that it complicates the picture

to use more than one ingredient for topical application because of the possibility of sensitivity reactions. If the patient does not respond promptly to the treatment instituted, cultures should be made or repeated and sensitivity tests done. All topical applications are limited to five days, after which the canal should be allowed to return to its normal physiologic state, i. e., an intact squamous epithelium and an acid pH. As an additional precaution against self-medication, McLaurin indicates on the prescription that it is not to be refilled and gives the patient carefully written instructions in order to be certain that the treatment will be carried out without individual deviations. All predisposing causes must be eliminated as far as possible.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

HEARING IMPAIRMENT IN PRESCHOOL-AGE CHILDREN. MIRIAM D. PAULS and WILLIAM G. HARDY, Laryngoscope **62**:534 (June) 1953.

Almost 600 infants and preschool children constitute this study. Although the average hearing loss for the whole group was 62 db., there was not one child with a total hearing loss. Recent developments have changed the whole picture. Galvanic skin-resistance audiometry enables the hearing threshold to be determined even in infants, and the modern hearing aid enables even those with a loss as great as 75 db. to use sound as a major pathway for language comprehension, provided, of course, that the proper management and training methods are instituted.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

MANAGEMENT OF CONGENITAL EAR-CANAL ATRESIA. HOWARD P. HOUSE, Laryngoscope **63**:916 (Dec.) 1953.

The difficult problem of congenital ear-canal atresia is clearly discussed. The operation to form a new canal and restore hearing is one of the most difficult in otology, particularly if sclerosis is present, and should be undertaken only after careful study.

If the condition is unilateral and there is hearing in the other ear, it is doubtful that the operation should be done. Also the presence of good cochlear function must be determined before operative procedures are undertaken.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

BILATERAL ABDUCTOR PARALYSIS OF VOCAL CORDS DURING LOCAL TONSILLECTOMY: REPORT OF A CASE AND ITS MANAGEMENT. GEORGE S. RICHARDSON, Laryngoscope **63**:1197 (Dec.) 1953.

Bilateral abductor paralysis of the vocal cords occurred during a local tonsillectomy. Novol (butethamine [Monocaine] hydrochloride, 1.5% with epinephrine, 1:100,000) was used as the anesthetic. There were no other untoward effects. The paralysis was relieved by the injection of 10 mg. of diphenhydramine (Benadryl) hydrochloride intravenously.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA. SAMUEL D. HEMLEY, AARON SCHWINGER, and ASA B. FRIEDMAN, New York J. Med. **53**:1861 (Aug. 15) 1953.

From the Department of Radiation, Kings County Hospital, Hemley and his associates report three cases of nasopharyngeal angiofibroma over a five-year period. It is a disease of childhood but is seldom diagnosed before adolescence! Pediatric literature is poor concerning it. Epistaxis and nasal obstruction are common signs. Erosion of the surrounding structures may cause irreversible pathology, although the growth is usually "benign." Because of bleeding, the taking of a biopsy specimen is a hospital procedure. One must differentiate between chordoma, choanal polyps, lymphoma, lymphoepithelioma, and fibroma. The tumor springs from the basisphenoid, averages 3 cm. in diameter, may grow rapidly, but does not metastasize

There is no true capsule, but a firm base. Microscopically, there is dense fibrous elastic connective tissue with high vascularity (veins). Surgery is indicated, but hemorrhage must be expected. Both external carotids are tied off as a preliminary step. Irradiation is useful but may limit normal growth of the bone, with resultant deformity of the face. Radon seeds hold no advantage over x-ray therapy. The androgen testosterone propionate, 25 mg. given four times a week, has been used in hypogonadal males, but its rationale may be questioned. There is no set rule for management—each case must be individualized. As to life, the prognosis is excellent, since the tumor regresses in adult life.

ABSTRACTOR'S COMMENT: If the tumor is supplied chiefly by veins, why ligate both external carotids? Has electrosurgery been tried? Are there any contraindications to this?

I. W. VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

STATISTICAL STUDY OF POSTOPERATIVE TONSIL AND ADENOID HEMORRHAGE. RICHARD J. BELLUCCI, New York J. Med. **53**:2495 (Nov.) 1953.

Bellucci made a statistical study at the Manhattan Eye, Ear and Throat Hospital of all cases of adenotonsillectomy admitted for ward service since 1948. Almost 20,000 (exactly 19,754) charts were reviewed of which there were 930 cases of primary hemorrhage and 208 cases of secondary hemorrhage. Weather conditions and the nationality, age, race, sex, and coloring of the patient seemed to have no bearing on the incidence of bleeding. History of a recent upper respiratory infection was not reflected in the expected increase of postoperative bleeding. But a higher incidence was recorded in the presence of carious teeth, mucopurulent discharge in the nose and throat, and large tender cervical lymph nodes. Tonsils which contained infected debris and those which were adherent to the fossae seemed to have more frequent hemorrhage after surgery. So-called "primary hemorrhages" were more often located in the nasopharynx after adenoid removal. Secondary bleeding was more often located in the tonsillar fossae. Surgical skill and patience in controlling bleeding are sine qua non of successful adenoid and tonsil surgery and postoperative results. Ninety-six per cent of the patients have shown general physical improvement after these operations. Postoperative bleeding after such operations can be reduced materially by removing or relieving all upper respiratory infections preceding surgery. Careful hemostasis before the patient leaves the operating table is imperative.

I. W. VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

LUPUS OF THE NOSE AND STREPTOMYCIN. F. CORDARO, Rev. otorinolaring. **12**:21 (April) 1952.

Cordaro presents four patients (13, 14, 30, and 48 years of age) with lupus of the nose. These were treated with dihydrostreptomycin in a dosage of 1 gm. daily for a period of seven to eight weeks. The results were extremely brilliant. All lesions were completely cured, and there was very little influence on either the vestibular or cochlear divisions of the eighth nerve. The mutilating treatment with either caustics or electrocoagulations has been definitely abandoned. Any other evidences of tuberculous toxemia were either favorably influenced or completely suppressed in the course of the treatment.

PERSKY, Philadelphia [A. M. A. ARCH. OTOLARYNG.]

LATENT SINUSITIS AS A FOCUS IN CHILDHOOD. E. K. SAUTER, Deutsche med. Wchnschr. **79**:1792 (Dec. 25) 1953.

The frequency of occult sinusitis in children is given as 8 to 63%, so that routine roentgen examination of the sinuses is regarded as desirable. It has an error of between 10 and 20%. Latent mucoid hyperplastic sinusitis occurs frequently in children of the 4- to 12-year age group, although no definite statistical material is offered. The maxillary sinus is mainly concerned. The role of the sinusitis as a focus is illustrated.

AMBERG, Rochester, Minn.

CLINICAL INVESTIGATION OF NERVE DEAFNESS DEVELOPING AFTER OTITIS MEDIA. I. KIRIKAE and Y. KITAYAMA, J. Oto-Rhino-Laryng. Soc. Japan **56**:429, 1953.

Fifty patients with nerve deafness, who had been previously well and who gave only the history of otitis media, were clinically investigated. There were two groups of patients. In the first group nerve deafness developed immediately after the acute otitis media subsided, and in the second group this form of hearing impairment developed at some interval after the episode of otitis media.

In the first group most of the patients showed high-tone deafness. This was thought to be due to tympanolabyrinthitis, without any symptoms of labyrinthine irritation. In the second group most cases showed high-tone deafness. In these cases it was suggested that the infection of the basal turn of the cochlea was due to the otitis media, which occurred later. Cases in which nerve deafness came on suddenly revealed a flat depression in the audiogram. The interval from the occurrence of otitis media to the onset of deafness did not exceed five years in the majority of patients in this group. Hereditary and constitutional predispositions were considered to play a part in the development of perceptive deafness. Kirikae and Kitayama emphasize the importance of treating children with otitis media as a preventive measure of deafness in adult life.

HARA, Los Angeles [A. M. A. ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura, and Mediastinum

THE BASIC LESION IN CHRONIC PULMONARY EMPHYSEMA. DAVID M. SPAIN and GERALD KAUFMAN, Am. Rev. Tuberc. **68**:24 (July) 1953.

The problem of pulmonary emphysema increases as more adults are able to reach the emphysematous ages, and persons in all age groups are maintained, by various antimicrobial agents, through pulmonary infections that formerly proved fatal. Since proper therapy depends on recognition of the basic defect, a reevaluation of the anatomic alterations in pulmonary emphysema was made by these investigators. The lungs of 10 men were examined post mortem. The evidence suggested that the bronchiolar defects (thickening, infiltration, narrowing, and elongation) were primary, and that the alveolar and parenchymal lesions were secondary to these obstructive phenomena.

ROYCE, San Marino, Calif.

CONGENITAL LUNG CYSTS IN INFANTS. HAROLD M. ALBERT and WILLIS J. POTTS, Pediatrics **12**:283 (Sept.) 1953.

The diagnosis and treatment of congenital lung cysts producing severe symptoms are discussed. The cases of six infants form the basis of this report. All had such severe dyspnea and cyanosis that emergency operations were necessary. All six infants made uneventful recoveries. The youngest child was 5 days old.

FROM THE AUTHORS' SUMMARY.

MYELITIS AFTER ATYPICAL PNEUMONIA. R. GOLDSTEIN, Helvet. paediat. acta **8**:107 (March) 1953.

Occasionally, myelitis may also be caused by generally nonneutrotropic virus diseases. A case is described of complete transverse myelitis in a 12-year-old boy, at the level of the fifth to the seventh thoracic segments, which followed a primary atypical pneumonia. There were no signs of meningitis or encephalitis, and the child recovered completely within 19 days. This is the third case in medical literature of myelitis after atypical pneumonia and the first one during childhood.

FROM THE AUTHOR'S SUMMARY.

AUTONOMOUS INFLAMMATORY BRONCHIAL STENOSIS IN AN INFANT. P. BRUSA and L. PARENZAN, Minerva pediat. **5**:845 (Oct. 15) 1953.

An 8-month-old baby was found to have recurrent respiratory febrile attacks traceable to a stenosis of the right upper bronchus, with atelectasis of the right upper lobe of the lungs.

HIGGINS, Boston.

THE CLINICAL RESULTS FROM DIAPNEUMOTHERAPY WITH PENICILLIN IN SOME DISEASES OF CHILDREN. M. MALASPINA, Minerva pediat. **5**:852 (Oct. 15) 1953.

Diapneumotherapy refers to the inhalation of a drug, in this study, penicillin, which has been nebulized into a small chamber containing the patient. Isuprel hydrochloride (Aleudrine) was also nebulized into the chamber in the cases of asthma or capillary bronchitis, where a bronchodilator was indicated. The clinical relief using this method of treatment was rapid and effective in a high percentage of the 74 cases reported.

HIGGINS, Boston.

CHLORAMPHENICOL (CHLOROMYCETIN), CHLORTETRACYCLINE (AUREOMYCIN), AND OXYTETRACYCLINE (TERRAMYCIN) IN CERTAIN RESPIRATORY INFECTIONS IN INFANCY. A. MIMO GALINDO, Arch. pediat., Barcelona **4**:81 (July-Aug.) 1953.

The author presents the detailed case histories of 26 infants treated for primary atypical pneumonia and pneumonias following chicken pox, measles, and whooping cough. All were young and presumably somewhat debilitated infants; several had rickets, and there had been other complications, including diarrhea and otitis media.

In the primary atypical pneumonia the author used chlortetracycline (Aureomycin), although he expressed the belief that the other antibiotics might have done as well. Penicillin had proved ineffective. For complications following pertussis the author advises chloramphenicol (Chloromycetin) in spite of the need to watch the blood cell counts in certain cases.

ALLEN, Santa Fe, N. Mex.

THE USE OF HYALURONIDASE IN THE TREATMENT OF PLEURAL EMPYEMA FOLLOWING UNRESOLVED PNEUMONIA. M. CRUZ HERNANDEZ and D. CABRERIZO PORTERO, Rev. españ. pediat. **9**:897 (Sept.-Oct.) 1953.

The authors give the details of therapy in six cases of empyema in children, using hyaluronidase intrapleurally. The antibiotic indicated from bacteriological study of the purulent material was also used. The combination of drainage, antibiotic, and hyaluronidase resulted in a swift recovery in all cases.

ALLEN, Santa Fe, N. Mex.

EMPYEMAS AND ABSCESSES OF THE LUNGS. F. HAMMER and J. SABACKY, Pediat. listy **8**:319, 1953.

The authors report 36 cases of pleural empyema and 11 cases of lung abscesses conservatively treated and healed. They show the influence of grippe infections on the occurrence of lung abscesses. Internal treatment on the basis of local application of a suitable antibiotic makes the surgical operation in most cases superfluous.

FROM THE AUTHORS' SUMMARY.

BULLOUS EMPHYSEMA IN CHILDHOOD. V. POKORNY, Pediat. listy **8**:329, 1953.

A series of seven cases of bullous emphysema in childhood between the ages of 10 months to 3 years is described. The radiographic appearance of this condition is described, and the views on its pathogenesis are summarized.

FROM THE AUTHOR'S SUMMARY.

HYPOPLASIA AND AGENESIS OF THE LUNG. J. W. C. DEGROOT and G. C. KWAKKELSTEIN, Maandschr. kindergeneesk. **21**:14 (Jan.) 1953.

A description of two cases of pulmonary hypoplasia is given; the first case presented an agenesis of the right lung in a baby girl. The second case presented a hypoplasia in an 8-year-old girl. The follow-up period was one year in the first case and seven years in the second. A survey of the literature is included.

FROM THE AUTHORS' SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

CHOLEDOCHAL CYST. E. H. DICKINSON and F. C. SPENCER, J. Pediat. **41**:462 (Oct.) 1952.

The patient was a 2-month-old white girl with a history of jaundice since 3 days of age and with persistent light-colored stools and dark urine. The liver was enlarged. There was no palpable tumor. At operation, a choledochal cyst was discovered. The surgeon anastomosed it to the duodenum. After six months the infant had no symptoms.

MACDONALD, Pittsburgh.

CARDIOCHALASIA IN INFANCY. W. DAVIES, J. Pediat. **41**:467 (Oct.) 1952.

Davies says that pure cardiochalasia starts at birth. The outstanding symptom is vomiting. Esophagitis possibly occurs in untreated cases. The condition may be recognized by x-ray screening with the patient in the Trendelenburg position following ingestion of a barium meal. Feeding the infant in an upright position seems to be an effective treatment.

MACDONALD, Pittsburgh.

BRONCHIAL OBSTRUCTION WITH LOBAR ATELECTASIS AND EMPHYSEMA IN CYSTIC FIBROSIS OF THE PANCREAS. PAUL A. DI SANT'AGNESE, Pediatrics **12**:178 (Aug.) 1953.

Lobar atelectasis with obstructive emphysema occurs in about 10% of patients with cystic fibrosis of the pancreas. In most instances, it appears in early infancy and during the first episode of pulmonary involvement; it usually affects one or more lobes of the right lung. It is an indication of severe respiratory disease, whose major expression is widespread obstruction of the bronchi and whose cardinal clinical features are cough, cyanosis, and respiratory distress. Rapid onset of bronchial obstruction due to failure to remove secretions is the initial event; infection is secondary and due to invasion of the obstructed bronchi.

The respiratory disease ushered in by lobar atelectasis represents one of the severer forms of fibrocystic disease of the pancreas; in many instances it is rapidly fatal unless checked in its progress by the use of antibiotics.

Bronchoscopy and bronchial aspiration through a tracheotomy tube are usually ineffective. Lobectomy is of doubtful value and is justified only by the persistence of lobar atelectasis unchanged for a prolonged period. Early diagnosis and early antibiotic therapy are at present the best weapons.

In infants below the age of one year, lobar atelectasis and obstructive emphysema, especially if they occur in white infants and involve the right lung, should suggest the possibility of cystic fibrosis of the pancreas.

The pathogenetic mechanism of the pulmonary lesions in cystic fibrosis of the pancreas is more acute and perhaps easier to understand in patients with lobar atelectasis but is essentially the same except in degree for all patients with this disease. Because of failure to remove the secretions, acute respiratory infections usually initiate the cycle by causing increased mucus production. Widespread and severe bronchial obstruction results, and secondary infection of the obstructed air passages follows after a variable but usually short period of time. If the patient survives the first episode, the same cycle can be repeated again on the occasion of a subsequent respiratory infection. Any one of these attacks can be fatal.

Although respiratory involvement is a virtually constant accompaniment of the pancreatic lesions in cystic fibrosis of the pancreas, their interdependence is still unexplained. The two principal theories regarding the interrelationship of the pulmonary and pancreatic lesions of fibrocystic disease are discussed. It is concluded that a satisfactory understanding of this problem has not yet been attained.

FROM THE AUTHOR'S SUMMARY.

CHRONIC INTUSSUSCEPTION IN CHILDREN. M. B. ABAD and ELEONORA P. DECANAY, Philippine J. Pediat. **2**:22 (April-June) 1953.

Chronic intestinal intussusception is much rarer than the acute intussusception. Only two cases were seen in the pediatrics department of Philippines General Hospital from 1930 to 1939, and only three cases from April, 1946, to February, 1952. These were observed in older children.

Three cases are herein reported. The symptomatology and diagnosis are described and discussed and compared with those of acute intussusception. A noteworthy point in the diagnosis of this condition is the common mistake of making a diagnosis of simple intestinal parasitism (ascariasis).

FROM THE AUTHORS' SUMMARY.

STRANGULATED SCROTAL HERNIA IN A BABY OF FIVE MONTHS. PIERO E. CARRAI, Riv. clin. pediat. **51**:112 (Aug.) 1953.

The author reports the occlusion of an inguinal hernia by a stercoroma contained in part of the small intestine in a boy 5 months old. There is no trace in medical literature of a comparable case.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF LARGE OMPHALOCELES. HERNÁN B. MADERO, Rev. mex. pediat. **22**:1 (Jan.-Feb.) 1953.

A new method is outlined for the treatment of large omphaloceles, which were considered practically inoperable. This procedure, first devised by Dr. R. E. Gross, of Boston, consists in burying the tumor under the skin and later on making a plastic repair of the abdominal wall. To the author's knowledge, it had never been used before, at least in Monterrey. One successful case is presented by the writer.

FROM THE AUTHOR'S SUMMARY.

ESOPHAGUS SURGERY IN CHILDHOOD. R. Wonke, Med. Klin. **48**:431 (April 3) 1953.

Within the frame of a survey of surgery of the esophagus an unusual case is reported. The history of the 4-year-old girl recorded a number of attacks of pneumonia since the age of 4 months. Variation was noted from well being without coughing and with good food intake to prolonged spastic attacks of coughing with profuse expectoration and refusal to take food. Finally, at roentgen examination the simultaneous appearance of contrast mass in trachea and esophagus was seen. At operation a fistula between the trachea and esophagus was seen. Its direction was oblique, and so that the tracheal opening was more cranial and that of the esophagus was more caudal. The surgical correction was successful.

AMBERG, Rochester, Minn.

Nervous Diseases

WHAT'S NEW IN CEREBRAL PALSY. MARGARET H. JONES, California Med. **79**:357 (Nov.) 1953.

Among new researches bearing on cerebral palsy are the growth of brain cells in tissue cultures for experimentation, the use of polysaccharides to prevent the formation of glial barrier to nerve growth after injury, the observation of changes in reactions of neurons at various stages of development, the finding of hypernatremia and hyperchloremia in lesions of the frontal lobe and the thalamus, the stimulation of cerebral blood flow by injection of sodium bicarbonate and the retardation with ammonium chloride, and studies of serial sections of brains of palsied children who died.

Study of development in the early months of life has made possible the detection of significant abnormalities in behavior early in life. Loss of hearing may be tested in very young children by measuring minute variations in electrical resistance of the skin upon auditory stimulation of the sympathetic nervous system.

Conditions which have been described as having been confused with cerebral palsy are dislocation of a cervical vertebra, hereditary spastic paraplegia, transverse myelopathy, injury to the spinal cord or cauda equina by anomalous growths of the spine, and, also encephalitis and meningitis.

Sedation has proved a valuable adjunct to electroencephalographic study of cerebral palsy. Better criteria for abnormality in the young child should be determined, and the application of them should be more clearly standardized.

Simple exercises are useful for early training of palsied children to stimulate development. "Crossed laterality"—the dominant eye being contralateral to the preferred hand—has been counteracted by special training with great success in eliminating emotional and behavior problems and accelerating development.

Recent studies indicate that only 50% of cerebral palsy patients have normal or better intelligence.

Subluxation of the hip joint, a common deformity associated with cerebral palsy, can sometimes be corrected by operation if detected at an early stage. Radical ablation of the epileptogenic foci in the cortex is also being done in young patients, if drug control of seizures fails. Frontal topectomy, cingulate gyrectomy, or prefrontal lobotomy may be advisable in cases in which proper response to drug therapy is not obtained.

Improvement in behavior as well as control of seizures may follow the use of amphetamine (Benzedrine), *d*-amphetamine sulfate (Dexedrine), diphenylhydantoin (Dilantin) sodium, mephobarbital (Mebaral) and phenobarbital. Alcohol, paraldehyde, and chloral hydrate have been effective as relaxants.

PRYOR, Redwood City, Calif.

INTRAVENOUS CHLORAMPHENICOL IN THE TREATMENT OF MENINGITIS DUE TO HEMOPHILUS INFLUENZAE (TYPE B). JOHN R. SCOTT and DWAIN N. WALCHER, J. Pediat. **41**:442 (Oct.) 1952.

The authors treated six patients with menigitis due to Hemophilus influenzae by intravenous injections of chloramphenicol. The dose was 50 mg. per kilogram per 24 hours, given in divided doses every 6 to 8 hours. The drug was diluted by adding it slowly, and with constant agitation, to from 100 to 150 cc. of 5% dextrose in distilled water. This solution was then introduced into the tubing of an infusion. Oral administration of chloramphenicol was begun after 60 hours, on an average. The patients recovered without any neurological abnormalities.

MACDONALD, Pittsburgh.

ORAL CHLORTETRACYCLINE (AUREOMYCIN) IN ACUTE PURULENT MENINGITIS IN CHILDREN. JULIO MENECHELLO and CARMEN AGUILO, Rev. chilena pediat. **24**:435 (Nov.) 1953.

Sixteen patients with purulent meningitis of different etiology are treated with chlortetracycline (Aureomycin) given orally. A cure with chlortetracycline exclusively was obtained in nine cases, two of which had sequelae (hemiplegia, subdural membrane). In seven cases, it was necessary to interrupt the administration of the drug, due to intolerance in one case; complete uselessness in two, and partial results in four. The results are analyzed and the possible causes of failure of chlortetracycline in some patients is discussed.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

COMPARISON OF POTENCY OF DIFFERENT ACTH PREPARATIONS BY INTRAVENOUS AND SUBCUTANEOUS ROUTES OF INJECTION. ROBERT W. BATES, Endocrinology **52**:266 (March) 1953.

The potencies of two different types of corticotropin (ACTH) preparations were compared by intravenous and subcutaneous injection, adrenal ascorbic acid depletion in the hypophysectomized rat being used as the criterion of potency. By the subcutaneous route of injection, as much as 100 to 1,000 times as large a total dose was required to cause equivalent ascorbic acid depletion as was needed by the intravenous route.

JACOBSEN, Buffalo.

COMPARISON OF THE EFFECTS OF CORTISONE ADMINISTERED INTRAPERITONEALLY AND SUBCUTANEOUSLY IN THE RAT. FRANCIS S. GREENSPAN, HOUGHTON GIFFORD, and QUENTIN B. DEMING, Endocrinology **52**:638-645 (June) 1953.

The data suggest that certain effects of cortisone acetate, such as loss in body weight and atrophy of the thymus and adrenal cortex, may require a sustained corticoid level, as may be produced by subcutaneous administration of the drug. Other metabolic effects, such as the restoration of water diuresis in the adrenalectomized water-loaded rat, occur rapidly following intraperitoneal administration of cortisone acetate, but, perhaps because of the shorter duration of the effective corticoid level, there is no inhibition of growth or production of adrenocortical atrophy.

JACOBSEN, Buffalo.

EXTRA ADRENAL EFFECT OF SOME COMMERCIAL PREPARATIONS OF CORTICOTROPIN UPON THE WORK PERFORMANCE OF THE HYPOPHYSECTOMIZED RAT. DWIGHT J. INGLE, JAMES E. NEZAMIS, and ERVING H. MORLEY, Endocrinology **53**:24-29 (July) 1953.

The capacity of the rat to work in response to the faradic stimulation of muscle is rapidly lost following either adrenalectomy or hypophysectomy. The data of this report show that adrenal cortex extract only partially supports the ability of either the hypophysectomized or the hypophysectomized-adrenalectomized rat to work, but that a combination of adrenal cortical extract with certain preparations of corticotropin fully sustains normal work performance of hypophysectomized rats in either the presence or absence of the adrenal glands.

These experiments indicate that the pituitary gland secretes a principle having an extraadrenal action upon body economy which is present in certain preparations of corticotropin and may or may not be identical with the principle(s) which affect body economy via the adrenal cortex itself.

JACOBSEN, Buffalo.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

PART PLAYED BY THE DIAPHYSIS IN THE PROCESS OF SKELETAL GROWTH AFTER THE GIVING OF SOME HORMONAL PREPARATIONS. G. COTELLESSA and A. DE MAESTRI, Minerva pediat. **5**:968 (Nov. 15) 1953.

In a previous article, the authors had shown that the growth of the long bones in rabbits was 75% referable to metaphyseal activity and 25% in the diaphysis itself. The observations with rabbits are now continued to learn how the giving of various hormones may affect the growth of the long bones. Testosterone propionate did not significantly affect normal bone growth. Thyroid gland greatly accelerated both the general and the diaphyseal bone growth. Anterior pituitary extract increased general bone growth, but did not influence the diaphyseal bone growth above that found in control animals.

HIGGINS, Boston.

LOCALIZED ACHONDROPLASTIC DYSTROPHY. A. ZAMORA SAMPER, Rev. españ. pediat. **9**:1073 (Nov.) 1953.

The author presents the case of an 11-year-old girl with deformities noted on closing the hands. X-ray showed deformities of the metacarpals in both hands similar to the type of changes noted in achondroplastic dystrophy. This was not noted in any other long bones of the body.

The author differentiates this condition from the conditions described in the literature, such as the Murk-Jansen syndrome, the Leri Weill, and others, and suggests calling it localized chondrodystrophy. He reports it because it is apparently very rare.

ALLEN, Santa Fe, N. Mex.

Diseases of Eye

ANALYSIS OF CONGENITAL NYSTAGMUS BY THE ELECTRO-NYSTAGMOGRAPHIC METHOD. A. FRANCESCHETTI, M. MONNIER, and P. DIETERLE, Bull. schweiz. Akad. med. Wissensch. **8**:403 (Nov.) 1952.

The author with his co-workers, improved the electro-oculographic and electronystagmographic method which he had developed for clinical purposes (Monnier and Hufschmidt, 1950, 1951). He recalls the principles of the electro-oculographic method which, by means of chains of bipolar leads, disposed vertically and horizontally around the eye, allows the analysis of horizontal, vertical, and rotary ocular movements. The deflexions registered with each of these movements are due to a change of distribution of the corneoretinal potential in the proximity of the eye. Given that the axis of the corneoretinal generator corresponds to the optical axis, each displacement of this axis produces a deflection which, by its direction and voltage, characterizes a definite movement of the ocular globe.

Having established the electro-oculographic characteristics of the elementary movements of each ocular globe, the author determined the optimal technical conditions for the electrophysiological analysis of the nystagmus. His electronystagmographic technique has the advantage of allowing an analysis of the nystagmus of each eye, the fixing eye as well as the closed eye (consensual nystagmus). It was possible, for instance, to analyze the variations of the optokinetic nystagmus with various postures of the eye.

The method also allows the recording of the vesibular nystagmus and is of practical interest for ophthalmology, neurology, and otology.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF CONGENITAL CATARACT. W. A. MANSCHOT, Maandschr. kindergeneesk. **20**:52 (March) 1952.

Monocular congenital cataract needs no treatment before the age of seven if the other eye has good visual function. In nearly all cases a postoperative amblyopia occurs which can not be prevented by an uncorrected aphakia. The use of contact lenses may perhaps alter this unpleasant situation.

Bilateral incomplete cataract should not be operated upon before the age of 7 years if vision is 20/60 or more.

There exists the greatest difference of opinion as to the optimum age at which cases of bilateral complete cataract should be operated on. Many authorities advocate operation on one eye in the first year and operation on the other eye in the third year. Functional results of operation on complete cataract are often bad, due to other congenital anomalies of the eye. Postoperative vision of 20/200 or better has been achieved in only approximately 50% of all cases. In discussing the situation with the parents one must always give a guarded prognosis with respect to vision, especially when other congenital anomalies are present.

Some of the usual operative procedures are discussed.

FROM THE AUTHOR'S SUMMARY.

Miscellaneous

SNAPPING THUMB IN INFANTS AND CHILDREN. J. A. BOLLINGER and J. J. FAHEY, J. Pediat. **41**:445 (Oct.) 1952.

The synonyms of this syndrome are trigger thumb and stenosing tendovaginitis of the flexor pollicis longus. The syndrome is less frequent in children than in adults. There is usually a fixed flexion contracture. In contrast to its incidence in adults, the "snapping" phenomenon seldom occurs in children.

The authors report this syndrome in twins, in one of whom the condition was bilateral. They note that the chief variance of the clinical manifestations of this syndrome in children is the greater tendency for locking and the less frequent incidence in the fingers. They report seven cases. Treatment is surgical.

MACDONALD, Pittsburgh.

PECULIAR CLINICAL APPEARANCE OF THE CONGENITAL NEUROBLASTOMA: SYNDROME OF MASSIVE METASTATIC DISSEMINATION IN CELLULAR TISSUE. MAURICE KAPLAN, RAYMONDE GRUMBACH, and PAUL VESIN, Presse méd., Supp. 67, p. 1350 (Oct. 21) 1953.

On the basis of a personal case and nine similar cases collected from the literature, the authors describe a new clinical syndrome caused by congenital neuroblastoma.

The cardinal features of the syndrome are (1) its peculiar clinical appearance, due to the extraordinary dissemination and to the location of the metastases from the neuroblastoma in the cellular tissue; (2) its occurrence in the very first weeks of life, and (3) its course—always rapidly fatal.

It may be assumed that in the future such an individualization will make it possible to recognize, through these clinical features, this special form of congenital neuroblastoma. Unfortunately, no therapy is so far worth being suggested for this condition.

FROM THE AUTHORS' SUMMARY.

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in New York, on April 30 and May 1 and 2, 1954.

Baldock, William E., Columbus, Ohio.
Barbero, Giulio John, Media, Pa.
Bennett, Sidney, Fresh Meadows, L. I., N. Y.
Berger, Harold Richard, Elizabeth, N. J.
Berman, Jerome David, Atlanta, Ga.
Blum, Alexander, Jr., Mount Kisco, N. Y.
Brown, David A., Darien, Conn.
Brown, Elizabeth Lillian, Long Island City, N. Y.
Burns, Arthur Eugene, Cleveland.
Calhoun, William Felix, Jr., Camp Rucker, Ala.
Cozzetto, Frank J., Boulder, Colo.
Crocker, Allen Carrol, Boston.
Cruise, Mary Ophelia, Jackson, Miss.
De Vito, Estelle Rose, New York.
Dorsey, William Rowlett, Salem, Mass.
Drorbaugh, James Edgar, Rochester, N. Y.
Eskwitt, Herbert Melvyn, New York.
Fanizzi, William J., Astoria, N. Y.
Farchione, Louis A., Syracuse, N. Y.
Farley, John Eugene, Jr., Riverside, R. I.
Felice, Anthony B., Brooklyn.
Gavenchak, Michael Joseph, Biloxi, Miss.
Gittelson, Stanley B., Cedarhurst, N. Y.
Goldblatt, H. William, Methuen, Mass.
Gollin, Pearl Reiffel, Chicago.
Griffiths, Sylvia Preston, New Haven, Conn.
Grumbach, Melvin Malcolm, Baltimore.
Hoffman, A. Charles, Queens Village, N. Y.
Hollander, Milton Henry, Brooklyn.
Huang, Nancy, Philadelphia.
Kangos, John James, New Brunswick, N. J.
Kaplan, Eugene S., Lynbrook, N. Y.
Koloski, Raymond, Poughkeepsie, N. Y.
Kuehn, Louis Frederick, Albuquerque, N. M.
Lame, Louis A., Cuyahoga Falls, Ohio.
Lethin, Anton Nathaniel, Jr., New Haven, Conn.
Ley, Joseph Charles, Pittsburgh.
Luetters, John Thielt, Hicksville, N. Y.
McDonald, Homer Jack, Birmingham, Ala.
Marshall, Florence, New York.
Maynard, Marian C., Oakland, Calif.
Mealy, Robert Francis, Taunton, Mass.
Mebane, Tom Sperring, State College, Pa.
Moyer, Winfield Tyson, Manchester, Conn.
Murphy, Thomas Joseph, Brockton, Mass.
Needham, Charles N., Syracuse, N. Y.
Neumann, Anna, Washington, D. C.
O'Donnell, George J., Wilkes-Barre, Pa.
Ogden, Neida Quackenbush, Cooperstown, N. Y.
Pascucci, Stephen E., Old Forge, Pa.
Phillips, Edgar Brownell, Boston.
Posner, David J., Levittown, N. Y.
Preston, Edmond, III, Moorestown, N. J.
Pulver, Nathaniel Joseph, White Plains, N. Y.
Randel, Harvey Oliver, New York.
Robison, William Harry, Roanoke, Va.
Roe, Arthur Allport William, Laconia, N. H.
Roy, Charles A., Southbridge, Mass.
Rusoff, Jerome H., Dobbs Ferry, N. Y.
Scalettar, Howard E., Sampson Air Force Base, N. Y.
Schrager, Gloria Ogur, Westfield, N. J.
Sell, Charles Gordon Rennick, New Orleans.
Shein, Joseph, Great Neck, L. I., N. Y.
Shinefield, Henry R., Paterson, N. J.
Sifontes, José E., Rio Piedras, Puerto Rico.
Slaughter, Bennie Celia, Dallas, Texas.
Smith, C. Warren, St. Thomas, V. I.
Spegal, Doris V., Dallas, Texas.
Stalonas, Anthony John, Brooklyn.
Strain, James E., Denver.
Szanton, Victor L., Ansonia, Conn.
Tella, Ralph Thomas, Stamford, Conn.
Terhune, Charles Bunnell, Summit, N. J.
Weiss, Howard, Chicago.
Wheeler, Harold Jens, Winchester, Mass.
Whoriskey, Frederick G., Cambridge, Mass.
Wong, Ruth, Paterson, N. J.
Wright, Lydia T., Buffalo.
Zahtz, Hyman, Flushing, N. Y.

ANNOUNCEMENTS

Coming Examinations to Be Held by The American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations on June 25, 26, and 27, 1954, in San Francisco, and on Oct. 8, 9, and 10, 1954, in Chicago.

New Members of Society for Pediatric Research.—At the meeting for the Society for Pediatric Research, which was held in Buck Hill Falls, Pa., on May 5, 6, and 7, the following were elected to membership in the society: Dr. Leonard Apt, Boston; Dr. William Bergstrom, Syracuse, N. Y.; Dr. Samuel Bessman, Washington, D. C.; Dr. Joseph Burchenal, New York; Dr. John Craig, Boston; Dr. Robert Ely, Salt Lake City; Dr. Harry Feldman, Syracuse, N. Y.; Dr. Lawrence Finberg, Baltimore; Dr. Samuel Foman, Cincinnati; Dr. F. C. Fraser, Montreal, Canada; Dr. Robert Kaye, Philadelphia; Dr. Benjamin Landing, Cincinnati; Dr. Bernard Laski, Toronto, Canada; Dr. Paul Lurie, Indianapolis; Dr. Donald Pickering, San Francisco; Dr. Charles Read, Winnipeg, Man., Canada; Dr. Nathan Smith, Los Angeles.

INDEXES

This issue of the JOURNAL appears in two parts, the second of which is the index for the preceding volume. To make the index more usable to the readers and to enable them to find information with less difficulty than has been encountered in previous volumes, the index has been broken down into three separate indexes: Title Index, Author Index, and Subject Index. The Title Index, which will take the place of the six-month Table of Contents, previously published with the index of the journals, has been prepared in such form that it can be separated from the other indexes and bound in the front of the volume. It consists of the titles of the articles arranged in alphabetical order and accompanied by the name of the author, the name of the senior author if there are more than two, the names of both authors if there are two, and the page number on which the article begins. The Author Index contains the names of all authors of articles appearing in the JOURNAL and of the presenters of cases or papers before societies. The third index, the Subject Index, contains in alphabetical order the important subjects which have been dealt with in the volume. Individual abstracts are no longer indexed; only the categories under which they have been classified are listed. Book notices and news items are included in this Index.

Directory of Pediatric Societies *

INTERNATIONAL

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 16 rue du Mont Blanc, Geneva, Switzerland.

IV° Congreso Pan-Americano de Pediatria

President: Dr. Leonel Gonzaga.
General Secretary: Dr. Adamastor Barbosa.
Secretariat: Rua Dias da Rocha 25, ap. 602, Copacabana, Rio de Janeiro.
Place: Rio de Janeiro. Time: 1954.

IV° Congreso Sudamericano de Pediatria, Confederacion Sudamericano de Sociedades de Pediatria

President: Prof. Carlos Prado.
Vice-President: Dr. Marcelo Garcia.
General Secretary: Dr. Alvaro Aguiar.
Place: Avenida mem de Sá 197, Rio de Janeiro. Time: 1954.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. Bernard Laski, Toronto.
Secretary: Dr. Crawford Anglin, Toronto.
Place: Academy of Medicine.

Asociación de Pediatras Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. P. A. Earnshaw, Ballow Chambers, Wickham Terrace, Brisbane. B17.
Honorary Secretary-Treasurer: Dr. D. C. Jackson, 217 Wickham Terrace, Brisbane. B17.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. J. Smellie.
Secretary: Prof. Alan Moncrieff, Institute of Child Health, The Hospital for Sick Children, Great Ormond St., W.C. 1, London.
Place: Windermere. Time: Between Easter and Whitsunday.

Canadian Paediatric Society

President: Dr. G. R. Gayman, 710 Seymour St., Vancouver 2, B. C.
Secretary-Treasurer: Dr. J. C. Rathbun, 526 Waterloo St., London, Ont.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital, Fûglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital, Martinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

Departamento de Pediatria da Associação Paulista de Medicina

President: Dr. J. Leme da Fonseca.
Secretary: Dr. Joaquim da Costa Marques.

Departamento de Puericultura e Pediatria da Associação Medica do Parana

President: Dr. Haroldo Beltrao.
Secretary: Dr. Mucio de Ãbreu Neto.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. Dr. med. O. Bossert, Städtische Kinderklinik, Essen.
Secretary: Prof. Dr. med. Jochims, Städtische Kinderklinik, Lübeck.
Place: Essen. Time: September, 1954.

Hellenic Society of Pediatrics

President: Dr. Spiros Charocopos, Alexandras Ave. 1, Athens.
Secretary: Dr. Nikas Zervos.
Place: Amphitheater, Medical School of the University of Athens. Time: Once a month.

Melbourne Paediatric Society

President: Dr. H. McLorinan.
Honorary Secretary: Dr. John H. Colebatch, 12 Collins St., Melbourne.
Place: Royal Children's Hospital, Melbourne. Time: Once monthly, February to December.

Nederlandse Vereeniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Roald Rinvik, Children's Department, Ullevål Hospital, Oslo.
Secretary: Dr. Bjarne Andersen, Children's Department, Ullevål Hospital, Oslo.
Time: Friday, six times a year.

Pediatric Society of New Zealand

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.

Philippine Pediatric Society

President: Dr. Renato Ma. Guerrero.
Secretary: Dr. Felix A. Estrada.
Place: Santo Tomas University Hospital and other pediatric centers. Time: Every two months.

Royal Society of Medicine, Section of Paediatrics

President: Dr. C. T. Potter.
Honorary Secretaries: Dr. A. P. Norman and Ursula James, M.R.C.P.
Sectional Editor: Dr. D. MacCarthy.
Place: 1 Wimpole St., London W.1 (Correspondence for these honorary officers should be sent to this address). Time: Fourth Friday of each month, 4:15 p.m.

Schweizerische Gesellschaft für Pädiatrie

President: P. D. Dr. F. Bamatter, St.-Léger 8, Genève.
Secretary: Dr. M. Nicod, Place Bel-Air 2, Lausanne.

Sociedad Argentinade Pediatrie

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviano de Pediatria

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedade Brasiliera de Pediatria

For officers, see IV° Congreso Sudamericano de Pediatria, above.

Sociedad Chihuahuensé de Pediatría

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatria

President: Dr. Jorge Camacho Gamba.
Vice-President: Dr. Antonio Alvarez Riaño.
Secretary: Dr. Hernando Vanegas A.
Treasurer: Dr. Efrain Perry Villate.

Sociedad Cubana De Pediatria

President: Prof. Agustin Castellanos y Gonzales.
Secretary: Dr. Carlos Hernandez Miyares, Apartado 2430, Habana.
Place: Catedra de Clinica Infantil Hospital Nuestra Senora de las Mercedes and Hospital Municipal de Infancia, Habana. Time: 9 p.m., last Wednesday of every month.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospital Clinico Reginal Concepción. Time: 7:30 p.m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litord

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatria y Puericultura del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Hernando Barrios-Angulo.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Bernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade de Puericultura e Pediatria do Maranbão

President: Dr. Odorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Sociedade Mineira de Pediatria

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

Sociedade Portugesa de Pediatria

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary-General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

Sociedad Uruguaya de Pediatria

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. H. Arroyo Parejo.
Vice-President: Dr. Manuel M. Lander.
Secretary: Dr. Guillermo Tovar E., P. O. Box 3122, Caracas.
Treasurer: Dr. Carlos Lares Compos.
Place: Hospital Municipal de Niños "J. M. de los Ríos," Caracas. Time: Once a month.

Sociedad Yucateca de Pediatria

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

La Société de Pédiatrie de Montréal

President: Dr. Henri Charbonneau, 3095 Sherbrooke, Montréal.
Secretary: Dr. Edmond Baril, 301 Carré St-Louis, Apt. 1, Montréal.
Time: Second Thursday of each month.

Société de Pédiatrie de Paris

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.
Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.
Place: Hôpital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p.m., third Tuesday of each month.

Société de Pédiatrie de Québec

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.
Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.
Place: Quebec. Time: May and November.

South African Paediatric Association

Chairman: Dr. Seymour Heymann, 804 Medical Centre, Jeppe St. Johannesburg.
Honorary Secretary-Treasurer: Dr. I. Kessel, Transvaal Memorial Hospital for Children, Milner Park, Johannesburg.

Swedish Association of Pediatrics

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Docent Urban Hjarne, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm, and Pediatric Clinic, Uppsala. Time: Second Friday of each month, except summer.

UNITED STATES

National

American Medical Association, Section on Pediatrics

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit.

American Academy of Pediatrics

President: Dr. Roger L. J. Kennedy, 102 2d Ave., S. W., Rochester, Minn.
Vice-President: Dr. Crawford Bost, 115 Terrace Dr., San Francisco 27.
Executive Secretary: Dr. E. H. Christopherson, 636 Church St., Evanston, Ill.
Treasurer: Dr. Edgar E. Martmer.

Society for Pediatric Research

President: Dr. Charles Janeway, Boston.
Vice-President: Dr. Wolf Zuelzer, Detroit.
Secretary-Treasurer: Dr. Sydney S. Gellis, Boston.

The American Pediatric Society

President: Dr. Rustin McIntosh.
Vice-President: Dr. Wilburt C. Davison.
Secretary-Treasurer: Dr. Aims C. McGuinness.

Sectional

Intermountain Pediatric Society

President: Dr. John T. Mason.
Secretary: Dr. Stanley R. Child.
Place: Ambassador Athletic Club, Salt Lake City. Time: 7 p.m.

New England Pediatric Society

President: Dr. Reuben C. Bates, 122 Waterman St., Providence, R. I.
Vice-President (President-Elect): Dr. Louis K. Diamond, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston, except Spring meeting. Time: Wednesdays, four times a year.

North Pacific Pediatric Society

President: Dr. Carl Ashley, 2455 N. W. Marshall St., Portland, Ore.
Secretary-Treasurer: Dr. S. Gorham Babson, 1107 S. W. 13th St., Portland, Ore

Northwestern Pediatric Society

President: Dr. F. G. Hedenstrom, 420 Lowry Medical Arts Bldg., St. Paul.
Secretary: Dr. Charles L. Steinberg, 1118 Lowry Medical Arts Bldg., St. Paul.
Place: Minneapolis; St. Paul; Duluth, Minn., and Rochester, Minn. Time: January, April, July, and October.

Rocky Mountain Pediatric Society

President: Dr. John Lichty, Pediatric Department, Colorado General Hospital, 4200 E. 9th Ave., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Announced by mail. Time: Monthly dinner meetings, October to June.

Southwestern Pediatric Society

President: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Carl A. Erickson, 960 E. Green St., Pasadena, Calif.
Place: Jonathan Club of Los Angeles. Time: 6:30 p.m., second Wednesday in January, March, May, September, and November.

Western Society for Pediatric Research

President: Dr. John Anderson.
Vice-President: Dr. Robert Aldrich.
Secretary-Treasurer: Dr. Forrest Adams.

State

Alabama Pediatric Society

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.
Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.
Place: Montgomery.

Arizona Pediatric Society

President: Dr. Henry E. Running.
Secretary: Dr. William F. Schaffman.
Time: On Call.

California Medical Association, Section on Pediatrics

Chairman: Dr. Joseph W. St. Geme, 511 S. Bonnie Brae, Los Angeles 5.
Secretary: Dr. Alvin H. Jacobs, 2201 Webster St., San Francisco 15.
Assistant Secretary: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills.

Florida State Pediatric Society

President: Dr. Charlotte C. Maguire, 1413 Kuhl Ave., Maguire Bldg., Orlando.
Secretary-Treasurer: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.

Georgia Pediatric Society

President: Dr. John A. Simpson, Athens.
Secretary: Dr. J. Harry Lange, 490 Peachtree St., Atlanta.
Place: Savannah. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Joseph Hetzel, 51 Central Ave., Waterbury.
Secretary: Dr. James H. Root Jr., 103 N. Main St., Waterbury.
Time: With the Connecticut State Medical Society in the spring, with the Connecticut State Clinical Congress in the fall; winter meeting usually in December.

Illinois State Medical Society, Section on Pediatrics

Chairman: Howard R. Miller, 418 Jefferson Bldg., Peoria 2.
Secretary: Harry H. Boyle, 2376 E. 71st St., Chicago 49.

Indiana State Pediatric Society

President: Dr. Harold D. Lynch, Evansville.
Secretary: Dr. L. T. Meiks, Indianapolis.

Iowa Pediatric Society

President: Dr. Charles J. Baker, 403 Carver Bldg., Fort Dodge.
Vice-President: Dr. P. E. Gibson, Davenport Pediatric Group, Davenport.
Secretary-Treasurer: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting. Fall meeting at University Hospital, Iowa City.

Massachusetts Hospital Association

President: Dr. Philip D. Bonnet, Administrator, Massachusetts Memorial Hospitals, Boston.
Executive Secretary: Henry G. Brickman, 14 Somerset St., Boston 8.

Michigan State Medical Society, Pediatric Section

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary: Dr. Park S. Bradshaw, 1014 Jefferson St., Muskegon.

Montana Pediatric Society

President: Dr. Orville M. Moore, 555 Fuller Ave., Helena.
Secretary: Dr. Joseph W. Brinkley, 410 Central Ave., Great Falls.
Place: Variable. Time: Spring and fall.

Nebraska Pediatric Society

President: Dr. Michael Crofoot.
Vice-President: Dr. Donald C. Nilsson.
Secretary-Treasurer: Dr. A. J. Lombardo, 401 Aquila Ct., Omaha.
Place: Children's Memorial Hospital. **Time:** 6 p.m., dinner, third Thursday of each month.

New Hampshire Pediatric Society

President: Dr. Margaret R. Reynolds, Windy Row, Petersborough.
Secretary: Dr. Wm. D. Penhale, 1 South St., Concord.
Place: Alternately Concord, Hanover, Laconia, and Manchester. **Time:** Four times a year.

New Mexico Pediatric Society

President: Dr. M. K. Wylder, Suite 14, Medical Arts Sq., Albuquerque.
Secretary: Dr. Ly Werner, Suite 25, Medical Arts Sq., Albuquerque.
Place: Variable. **Time:** Every two or three months.

North Carolina Pediatric Society

President: Dr. Robert A. Moore, 1505 Elizabeth Ave., Charlotte 4.
Secretary-Treasurer: Dr. Fred R. Cochran, 1361 E. Morehead St.
Place: Roaring Gap and Chapel Hill. **Time:** Sept. 12 and Oct. 30, respectively.

South Carolina Pediatric Society

President: Dr. Walter Moore Hart, 117 W. Cheves St., Florence.
Secretary: Dr. John R. Paul Jr., 82 Rutledge Ave., Charleston.
Place: Columbia, S. C. **Time:** Second Monday and Tuesday in September.

Tennessee Pediatric Society

President: Dr. O. L. Von Canon, 846 McCallie Ave., Chattanooga.
Secretary: Dr. Oliver W. Hill, 4807 Newcom Ave., Knoxville.

Texas Pediatric Society

President: Dr. Robert L. Moore, Dallas.
President-Elect: Dr. M. C. Carlisle, Waco.
Secretary: Dr. James N. Walker, Fort Worth.
Treasurer: Dr. Jack M. Woodall, Big Springs.

Virginia Pediatric Society

President: Dr. Edwin L. Kendig Jr.
Secretary: Dr. T. J. Humphries.

Wisconsin State Medical Society, Section of Pediatrics

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. **Time:** 8:15 p.m., October, December, February, and March.

Baltimore City Medical Society, Pediatric Section

President: Dr. Wilson Grubb, 4 E. 33d St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.
Place: 1211 Cathedral St., Baltimore 1. Time: 8:30 p.m., second Tuesday in November, January, and March.

Bronx Pediatric Society

President: Dr. M. H. Grand, 1749 Grand Concourse, New York.
Secretary: Dr. Charles T. Fried, 1220 Grand Concourse, New York.
Place: Morrisania City Hospital. Time: 8:30 p.m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn.
Secretary: Dr. Henry Cohen, 1761 E. 19th St., Brooklyn.
Place: Granada Hotel, Brooklyn. Time: 8:45 p.m., fourth Wednesday of February, March, April, October, and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold.
Secretary: Dr. Richard A. Downey.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p.m., first Monday of each month, September to June.

Central New York Pediatric Club

President: Dr. Frank Williams, 58 Swan St. S., Albany.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.
Place: Various cities in New York State; fall meeting jointly with Upper New York State Academy of Pediatrics. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. O. W. Hosterman, 350 East Broad St., Columbus 15.
Secretary-Treasurer: Dr. John Riepenhoff, 2998 Sullivant Ave., Columbus.
Place: As announced. Time: Third Wednesday of September, November, January, March, and May.

Chicago Pediatric Society

President: Dr. Eugene T. McEnery.
Vice-President: Dr. Maxwell P. Borovsky.
Secretary: Dr. Ralph H. Kunstadter, 104 S. Michigan Blvd.
Treasurer: Dr. Noel G. Shaw.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Joseph E. Ghory, 2546 Auborn Ave.
Secretary: Dr. Clare R. Rittershoffer, 301 Erkenbrecker.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. Edwin A. Danford.
Secretary: Dr. Jack F. McKemie.
Place: As announced. Time: 7:30 p.m., fourth Wednesday of January, March, May, July, September, and November.

Dade County Pediatric Society

President: Dr. Lynn Whelchel, DuPont Bldg., Miami, Fla.
Secretary: Dr. Howard Engle, 311 Lincoln Rd., Miami Beach, Fla.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.
Place: Children's Hospital of Texas. Time: 6:30 p.m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Wolf Zuelzer.
Secretary: Dr. Mario S. Cioffari.
Place: Variable. Time: Five times a year.

Honolulu Pediatric Society

President: Dr. John Peyton, Medical Group, 1133 Punchbowl St.
Recording Secretary: Goonzo Yamashita, 1618 S. King St.
Corresponding Secretary-Treasurer: Dr. H. M. Sexton, Straub Clinic, 1020 Kapiolani St.
Place: At doctors' homes in rotation. Time: 6 p.m., third Thursday of each month.

Houston Pediatric Society

President: Dr. David Schrum, 5101 Fannin St., Houston.
Secretary: Dr. Juanita Thacker Hart, 306 South 7th St., Bellaire.
Place: River Oaks Country Club. Time: 6:30 p.m., fourth Tuesday of each month.

Kansas City Southwest Pediatric Society

President: Dr. Frank Hogue, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.
Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.
Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.
Secretary: Dr. Arthur J. Holmes, 65 N. Madison Ave., Pasadena 1.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd., Los Angeles.
Time: Second Thursday of alternate months beginning in September.

Louisville Pediatric Society

President: Dr. Harry S. Andrews.
Vice-President: Dr. Joseph Little.
Secretary-Treasurer: Dr. Kenneth P. Crawford.
Place: Variable. Time: Five times a year, as announced.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn.
Secretary: Dr. Bernard Greenberg, 755 Ocean Ave., Brooklyn 26.
Treasurer: Dr. David Dragutsky, 1466 49th St., Brooklyn.
Place: Kings County Medical Society Auditorium, 1313 Bedford Ave., Brooklyn. Time: 8:45 p.m., fourth Monday of January, March, April, October, and November.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington 20.
Secretary: Dr. John E. Cassidy, 5402 Connecticut Ave. N.W., Washington.
Place: Medical Society Bldg., 1718 M St. N.W., Washington. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Clifton W. Woolley, 2448 Poplar Ave.
Vice-President: Dr. Steve H. Turnbull, 848 Adams.
Secretary-Treasurer: Dr. Charles H. Householder, 321 S. Bellevue.
Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday of each month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. Franklin Mellencamp, 1513 E. Capitol Dr., Milwaukee.
Secretary: Dr. Karl Beck, 1411 Wauwatosa Ave., Milwaukee.
Place: Milwaukee University Club. Time: Second Wednesday of February, April, June, and October.

MOBILE PEDIATRIC SOCIETY

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.
Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. Thomas Weaver, Bennie Dillon Bldg., Nashville, Tenn.
Secretary: Dr. Ethel Walker, 3415 West End Ave., Nashville, Tenn.
Place: Homes of members. Time: Third Thursday of every month.

NASSAU PEDIATRIC SOCIETY

President: Dr. Mildred Wicker Jackson, 254 South St., Oyster Bay, N. Y.
Secretary: Dr. David J. Posner, 98 Wolcott Rd., Levittown, N. Y.
Place: Pending; contact Levittown 3-6666. Time: 7:30 p.m., second Monday of October, December, February, April, and June.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. Jerome L. Kohn, 50 W. 96th St., New York 25.
Secretary: Dr. Lawrence B. Slobody, 1 E. 105th St., New York 12.
Place: New York Academy of Medicine, 2 E. 103d St. Time: 8:30 p.m., second Thursday of each month, November to May, inclusive.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. Edward Campion, 707 C St., San Rafael.
Secretary-Treasurer: Dr. Joseph H. Davis, 300 Homer Ave., Palo Alto.
Place: San Francisco. Time: Quarterly, as speakers are available.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. C. M. Bielstein, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Louis Frank, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. Charles C. Chapple, 1740 Bainbridge St., Philadelphia 46.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Christian John Stoecklein, 519 Medical Arts Bldg., Pittsburgh 13.
Secretary-Treasurer: Dr. James W. Stirling, 694 Lincoln Ave., Pittsburgh 2.
Place: Western State Psychiatric Institute and Clinic. Time: Second Friday in October, December, February, and April.

Queens Pediatric Society

President: Dr. Moe Goldstein, 111-32 76th Ave., Forest Hills, N. Y.
Secretary: Dr. John Finnegan, 36-19 Bowne St., Flushing, N. Y.
Place: Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.
Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

San Antonio Pediatric Society

President: Dr. Philip Magrish, 402 Fulton Ave.
Secretary: Dr. Jack M. Wright, 403 Summit Ave.
Time: 7:30 p.m., supper, first Tuesday of each month.

St. Louis Pediatric Society

President: Dr. H. E. Wachter, 8505 Delmar.
Vice-President: Dr. Raymond J. LaDriere, 35 No. Central, Clayton 5, Mo.
Secretary-Treasurer: Dr. Leo F. Gowen, 337 W. Lockwood, Webster Groves 19, Mo.
Place: Medart's Restaurant. Time: 7 p.m., second Thursday of each month from September to May, inclusive.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.
Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara, Calif.
Place: Varies. Time: Two to three times yearly, on call.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Fred J. Chapin, 101 John St., Bay City.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.
Place: University Hospital, Ann Arbor.

Waco Pediatric Society

President: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.
Secretary: Dr. C. G. Shellenberger, 1318 Austin Ave., Waco, Texas.
Place: 1917 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

President: Dr. Herbert Kahan, 650 Main St., New Rochelle, N. Y.
Secretary: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Four dinner meetings a year, November, February, April, and June.

Western Michigan Pediatric Society

President: Dr. A. Morgan Hill, 310 Fulton, E., Grand Rapids.
Secretary: Dr. John C. Montgomery, 1810 Wealthy St., S.E., Grand Rapids.
Place: Two meetings in Grand Rapids, two elsewhere. Time: First Wednesday of October, November, April, and May.

Wichita Pediatric Society

President: Dr. Frank L. Menehan.
Secretary: Dr. R. C. Knappenberger.
Place: Homes of members. Time: 8:30 p.m., first Thursday, October through May.

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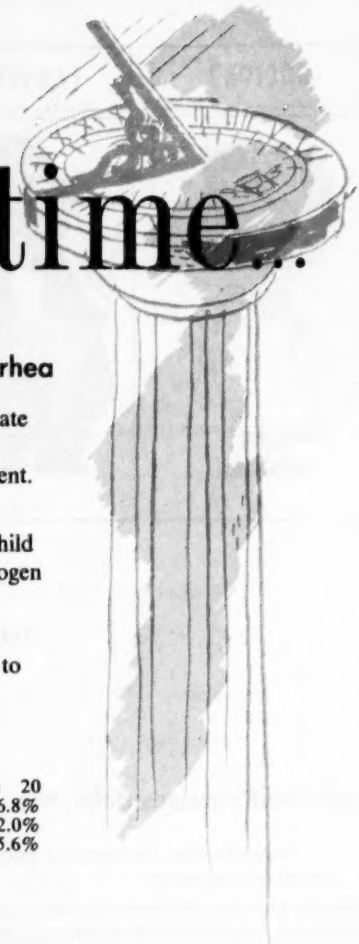

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Water—6 ounces

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Calories per fluid ounce	20
Protein	6.8%
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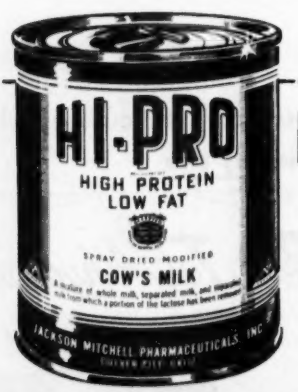
[1]Jeans, P. C. & Marriott W. McK. Infant Nutrition; 4th ed.
[2]Holt, E. M. Diseases of Infancy; 11. 223.



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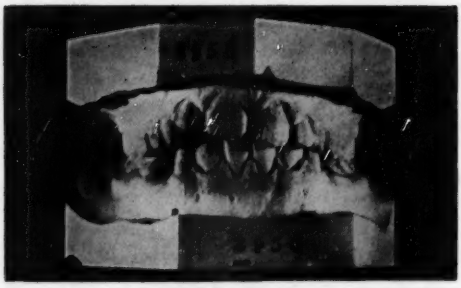

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Though it is universally accepted that protein nutrition deserves special emphasis in childhood, the possibility of protein deficiency in children rarely receives adequate attention.[1] As shown by creatinine excretion, children frequently are deficient in muscle mass. Through improved protein nutrition muscle mass in these children often can be increased by as much as 25 per cent without increasing body weight, thus demonstrating that fat is being replaced with muscle tissue.[2]

Vigilant heed is necessary to assure that children get enough of foods supplying an abundance of biologically adequate protein and of vitamins and minerals. Rapid growth and the great activity of children make the demand for these nutrients and for calories even more urgent than in adults.

Surveys show that faulty eating habits largely are responsible for the high incidence of nutritional deficiency and anemia in school children.[3] Among commonplace practices carrying such nutritional hazards are small, poorly chosen breakfasts or omission of the morning meal; the selection of foods left to discretion of the child; overindulgence in foods and drinks providing calories but little of protein, vitamins, and minerals; failure to eat meat or equivalent foods in adequate quantity; and the eating of insufficient amounts of vegetables and fruits.[4]

Meats should be a regular item in the diet of children,[5] not only for its notable contribution of top-quality protein, but also because meat furnishes important amounts of B vitamins—thiamine, riboflavin, and niacin—and of minerals, including iron, potassium, and phosphorus.

---

1. Jeans, P. C.: Feeding of Healthy Infants and Children, J.A.M.A. *142*:806 (Mar. 18) 1950.

2. Flodin, N. W.: Amino Acids and Proteins, Their Place in Human Nutrition Problems, J. Agr. & Food Chem. *1*:222 (Apr. 29) 1953.

3. Nutrition of School Children, Editorial, J.A.M.A. *128*:1233 (Aug. 25) 1945.

4. Boyd, J. D.: The Need for Betterment of Children's Diets, J. Am. Dietet. A. *20*:147 (Mar.) 1944.

5. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, 6th ed., Philadelphia, W. B. Saunders Company, 1952, p. 214.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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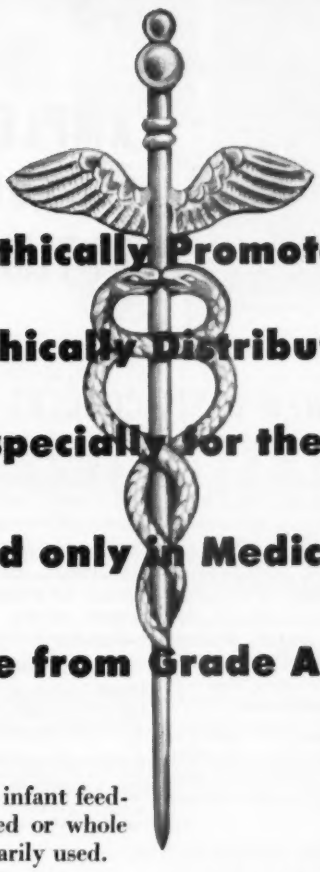

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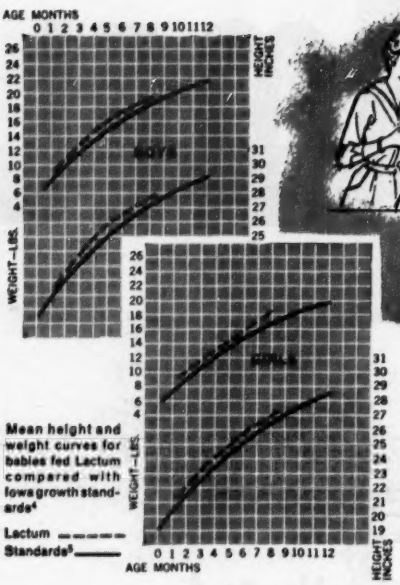

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(1) Jeans, P. C.: In A.M.A. Handbook of Nutrition, Ed. 2, Philadelphia, Blakiston, 1951, p. 275. (2) Albanese, A. A.: Pediat. 8: 456, 1951. (3) Holt, L. E., Jr., and McIntosh, R.: In Holt Pediatrics, Ed. 12, New York, Appleton-Century-Crofts, Inc., 1953, pp. 175-178. (4) Frost, I. H., and Jackson, R. L.: J. Pediat. 30: 585, 1951. (5) Jackson, R. L., and Kelly, H. G.: J. Pediat. 27: 215, 1945.

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1. Lewis, J. M., et al.: Jl. Pediatrics 31:496, 1947
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5. Clifford, S. H. and Weller, K. H.: Pediatrics 1:505, 1948
6. Popper, H., et al.: Gastroenterology 10:987, 1948
7. Davidson, D. M., et al.: Jl. Invest. Derm. 12:221, 1949
8. Nutrition Reviews 6:248, 1948

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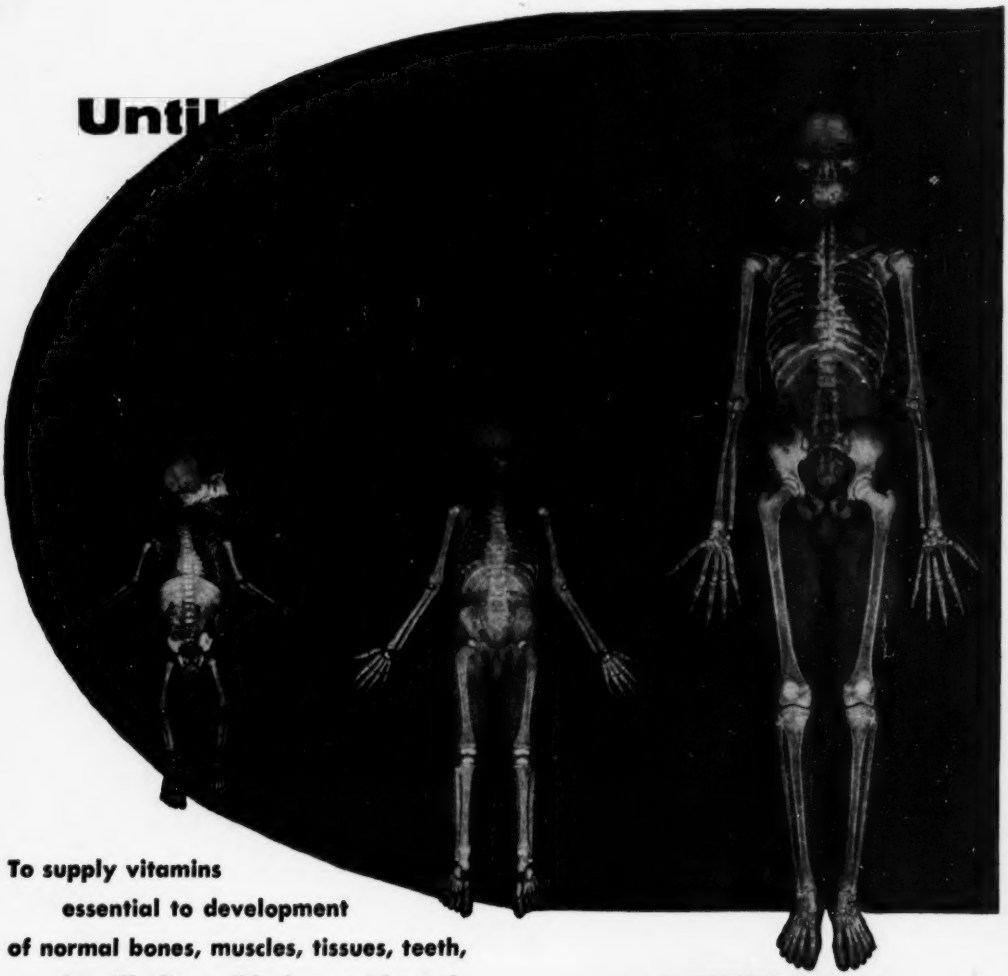

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